Synthesis of Pyridone Building Blocks for Biomimetic Complexes of Mono-Iron Hydrogenase

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In partial fulfillment of the requirements for graduation with the Dean's Scholars Honors Degree in Chemistry

University of Texas at Austin

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Department: Chemistry

Tim Sotman

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Signature Date

Dr. Michael J. Rose

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Abstract

Hydrogen gas is a promising alternative to conventional fuels like coal or gasoline because it can be produced from water. The most effective catalysts for the reduction of water to hydrogen are based on palladium and platinum—precious, expensive metals—but the search for catalysts based on the more abundant transition metals (e.g. Co, Fe, and Ni) is ongoing. Chemists have turned to biological catalysts—enzymes like mono-iron hydrogenase—for guidance in the design of transition metal-based hydrogen activation catalysts. Mono-iron hydrogenase activates H_2 by cleaving it heterolytically, resulting in H^+ and a hydride (H^-) which is transferred to a hydride carrier molecule called methenyltetrahydromethanopterin (methylene-H_4MPT). The mono-iron hydrogenase active site contains an iron center complexed to two carbonyls and an acyl-pyridone ligand conjugated to a guanine nucleotide by a phosphodiester bond. The iron cofactor is connected to the enzyme by only one covalent association: the cysteine amino acid ligand. The work described in this thesis relates to the synthesis and characterization of a series of pyridone compounds to be used in ligands that mimic the chemical environment of the mono-iron hydrogenase active site in small-molecule iron complexes. Biomimetic iron complexes synthesized using these ligands may shed some light on the catalytic mechanism of the mono-iron hydrogenase enzyme and may themselves be capable of useful catalysis. A series of 3-Br, N- and O-protected pyrone and pyridone coupling partners and a collection of trifluoromethylated pyridone derivatives have been synthesized, and the synthesis of an unreported 5-methyl pyridone is proposed.

Dedication

Dr. James Aldridge

August 31, 1953—April 26, 2014

This thesis is dedicated to Dr. Jim Aldridge, the man who initially sparked my interest in Chemistry. Dr. Aldridge taught my Sophomore Honors Chemistry, AP Chemistry, and AP Computer Science courses in highschool. Always patient, he was an intellectual sounding board for my developing ideas and opinions, absurd or otherwise. But, more importantly, I owe him a debt of gratitude for his mentorship outside the classroom, where he encouraged my love of camping and cycling. A multifaceted man of many talents, he was the kind of guy who would claim the facebook URL facebook.com/fluorine for himself, water his greenhouse full of orchids, and then hop on his Aprilia Tuono motorcycle for a ride through the Weatherford backroads. I'm sorry to see him go. He will be missed.

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Introduction

Hydrogen gas is a promising alternative to conventional fuels like coal or gasoline because it can be produced from water using solar energy.[1] The most effective catalysts for the reduction of water to hydrogen are based on palladium and platinum—precious, expensive metals—but the search for catalysts based on the more abundant transition metals (e.g. Co, Fe, and Ni) is ongoing.[2] Luckily, nature has already solved the problem of hydrogen activation using common metals at least three independent times. Three phylogenetically unrelated families of hydrogenase enzymes have evolved over time to meet this need in a number of anaerobic organisms.[1] The three major classes of hydrogenase enzymes are the iron-nickel hydrogenases, the iron-iron hydrogenases, and mono-iron hydrogenase. The active sites of each of the dinuclear hydrogenase enzymes are pictured in Figure 1. Chemists have looked to these enzymes for guidance while designing so-called bimimetic, small-molecule catalysts that perform the same function: hydrogen activation. A relatively large body of research relating to the dinuclear (iron-nickel and iron-iron) hydrogenases exists, and some of these catalysts have proven active in the desired reaction, but these biomimics are usually spoiled by contact with air.[3] Comparatively little research has been done to mimic the active site of mono-iron hydrogenase. Mono-iron hydrogenase is a promising model for small molecule catalysts because the mono-iron hydrogenase active site (Figure 2) contains a single metal center rather than the more complicated, dinuclear, iron-sulfur cluster containing active-sites of the other hydrogenase families (Figure 1). Furthermore, biomimetic catalysts modeled after mono-iron hydrogenase may demonstrate greater stability in air in comparison to the dinuclear counterparts.

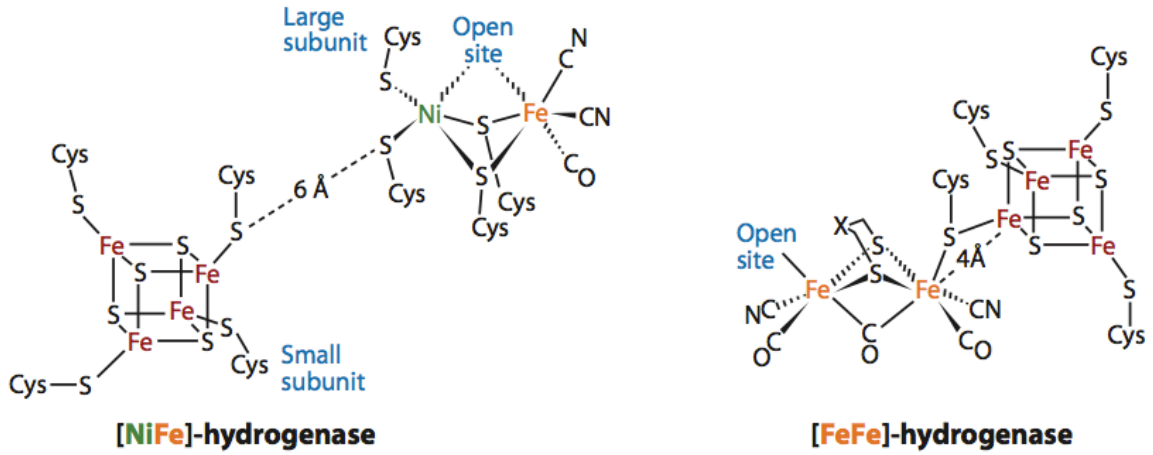


Figure 1. The active sites of iron-nickel hydrogenase and iron-iron hydrogenase are characterized by their dinuclear, thiolate-bridged structure, the presence of both cyanide and carbonyl groups, and the presence of iron-sulfur clusters.[1]

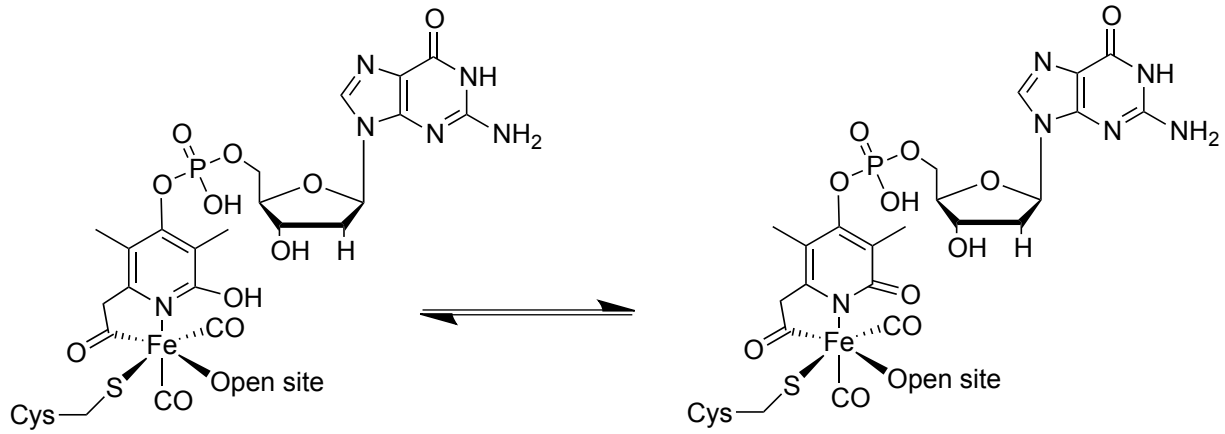


Figure 2. The mono-iron hydrogenase active site contains an iron center complexed to two carbonyls and an acyl-pyridone ligand conjugated to a guanine nucleotide by a phosphodiester bond. The iron cofactor is connected to the enzyme by only one covalent association: the cysteine amino acid ligand.[4, 5]

The mono-iron hydrogenase active site (Figure 2) iron is surrounded by a number of covalently bound compounds called ligands. These ligands—including a unique pyridone cofactor—alter the chemical environment of the iron center, enabling the metal to participate in the chemical reactions that lead to hydrogen activation. The work described in this thesis relates to the synthesis and characterization of a series of pyridone compounds to be used in ligands that mimic the chemical environment of the mono-iron hydrogenase active site. The conceptual

framework of this process is summarized in Figure 3. Biomimetic iron complexes synthesized using these ligands may shed some light on the catalytic mechanism of the mono-iron hydrogenase enzyme and may themselves be capable of useful catalysis.

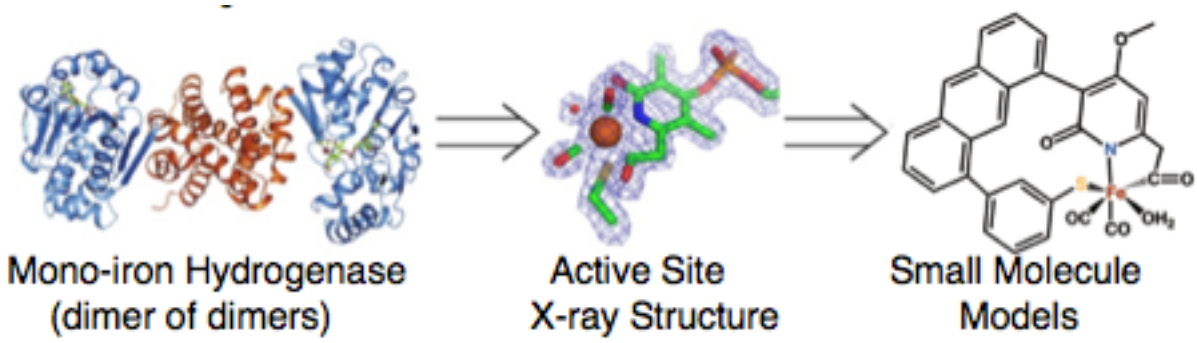


Figure 3. The iron-complexing active site of the mono-iron hydrogenase can be modeled in the form of small-molecule iron complexes with ligands that mimic the chemical environment of the enzyme.[7]

Background

Hydrogen is the most abundant element in the universe, but molecular hydrogen is not found in significant molecular concentrations on Earth. Whereas most hydrogen throughout the universe is in the form of H_2, the majority of hydrogen on Earth is usually present as water or in hydrocarbon compounds.[2] The production of H_2 from these sources is of interest not only because it may be used for hydrogenation reactions, but also because it could be used as a fuel. Most industrially produced hydrogen gas is derived from fossil fuel hydrocarbons by steam reformation of natural gas or gasification of coal.[2] Alternatively, H_2 may be obtained from water by applying a voltage to electrolytically cleave the water into hydrogen and oxygen.[1] In contrast with fossil fuel sources, water is a promising renewable source of H_2. Some technical hurdles must be overcome before electrolytically produced hydrogen can begin to play a viable role in the energy economy, however.

In comparison to conventional fuels like gasoline, liquefied hydrogen is considerably less energy dense. In other words, the amount of energy available in a given volume of hydrogen is much smaller than the amount of energy that can be obtained from an equal volume of gasoline.[1] Because of the increase in sheer volume of fuel that would be consumed in a hydrogen based energy economy, the cost of fuel transportation would be prohibitive. Ongoing research seeks to develop solid materials that can store hydrogen in a more energy-dense manner, however an alternative solution is more likely. To solve the problem of transportation cost, electrolytically produced hydrogen could be used as a feedstock in the manufacture of a hydrocarbon energy carrier.[1] Hydrogen activation catalysts will be necessary to generate these combustible, reduced-carbon fuels (HCOOH, CH_3OH, iPrOH) from substrates like CO_2 or an other carbon carrier. If H_2 is to become a contender in the alternative energy arena, cheaper hydrogen generation catalysts and more efficient CO_2 reduction catalysts must be developed. A great deal of time and energy is currently being invested in research to meet these needs, and often the inspiration for these developments comes from unlikely places.

Several unicellular organisms have independently evolved enzymes which either allow them to use H_2 as an energy source (methanogenic archaea) or use H^+ as the terminal electron acceptor thus generating H_2 (bacteria).[1] These enzymes are called hydrogenases because their main role is activation of the H-H bond. Three distinct classes of hydrogenase enzymes are known: iron-iron hydrogenase (Figure 1), iron-nickel hydrogenase (Figure 1), and mono-iron hydrogenase (Figure 2). Each of these enzymes catalyzes the breakdown of H_2 at the location on the protein, called the active site, where a catalytically active metal complex resides. In an effort to design catalytically active metal complexes that mimic the active sites of the hydrogenase enzymes but do not contain the complication of the surrounding protein, scientists have

synthesized a number of *biomimetic* complexes. Many complexes having structures that mimic the active sites of iron-iron hydrogenase and iron-nickel hydrogenase have been synthesized.[3] Complexes modeled after these dinuclear hydrogenases suffer from sensitivity to oxygen, however, because they contain both thiolates and iron sulfur clusters (Figure 1).[3] In comparison to the dinuclear hydrogenase enzymes, the third type of hydrogenase enzyme, mono-iron hydrogenase, has been not been modeled extensively.

Mono-iron hydrogenase occurs naturally in methanogenic archaea like *Methanocaldococcus janischii*, which use H_2 as an electron source for the eventual reduction of CO_2 to methane, CH_4.[1] These organisms use a unique hydrogenase enzyme containing a single iron center in each of the two active sites of the homodimeric protein (Figure 3). Because each catalytic center contains only one iron atom, the enzyme is called the mono-iron hydrogenase. Mono-iron hydrogenase activates H_2 by cleaving it heterolytically, resulting in H^+ and a hydride (H^-) which is transferred to a hydride carrier molecule called methenyltetrahydromethanopterin (methenyl-H_4MPT).[6] Because this heterolytic cleavage is reversible, small molecule mimics of the mono-iron hydrogenase enzyme should be able to catalyze the reverse reaction: production of H_2 from H^+ and a H^- donor. Other related iron complexes may function in a manner similar to the original hydrogenase enzyme, using H_2 to reduce CO_2 or another carbon source to produce formate, CO, methanol or other compounds more useful than CO_2, as described previously.[1] Application of cheap, iron-based catalysts modeled after the mono-iron hydrogenase enzyme in a CO_2 reduction pathway in an industrial setting could not only significantly reduce greenhouse emissions, but would also generate value-added products for industrial processes.

Because the mono-iron hydrogenase enzyme was discovered relatively recently (1990), the mechanism of its catalysis is not well understood.[1] A deeper understanding of the catalytic

mechanism would aid in the rational design of small molecule mimics that exhibit comparable catalytic action. Typically, enzymatic mechanisms are studied by producing single amino acid mutations in the wild type enzyme and observing the effects on catalytic parameters (e.g. K_m, k_{cat}, V_{max}, etc). However, the structure of the mono-iron hydrogenase enzyme does not lend itself to this kind of biochemical mutation because only one amino acid (Cys 176) participates in ligation of the Fe center.[7] The other ligands surrounding iron—including the pyridone cofactor and two carbonyl groups—are not covalently bound to the protein. They are only associated with the enzyme by their ligation to the Fe center. Because biochemical mutation would not allow much variation of the primary coordination sphere, a technique called *synthetic mutation* is proposed to allow the catalytic mechanism of the enzyme to be studied.[8] Synthetic mutation involves the introduction of a chemically pre-modified pyridone cofactor to the apoenzyme—the enzyme without its cofactor. This process of reconstituting an active holoenzyme from the heterologously produced apoenzyme and the wild-type iron-pyridone cofactor has been proven possible by Shima et al.[2] Currently, several modified pyridones can be prepared and are promising candidates for such an approach (see discussion). Introduction of the chemically modified pyridone cofactor will lead to altered catalytic behavior in the reconstituted enzyme. We hypothesize that synthetic mutations will reveal details of the catalytic mechanism.

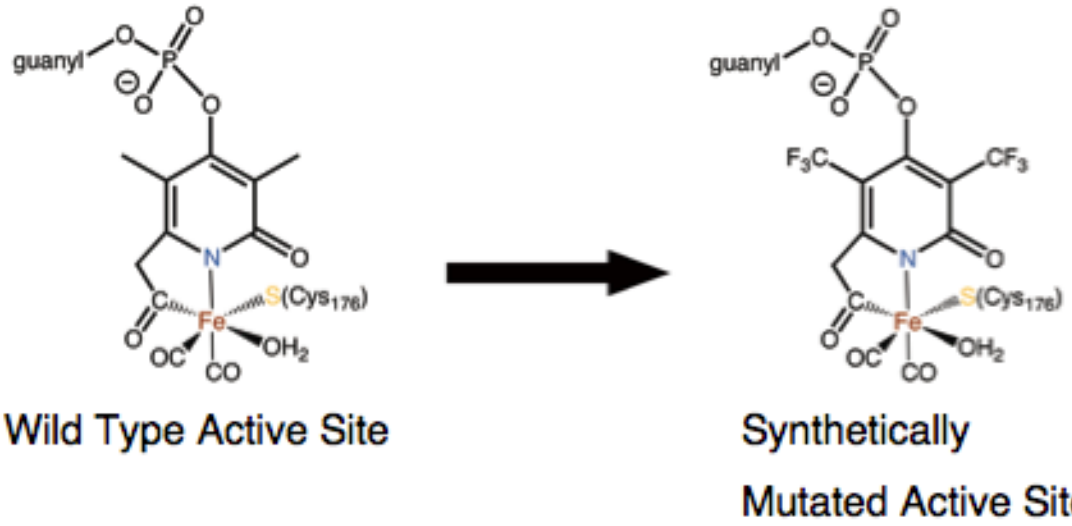
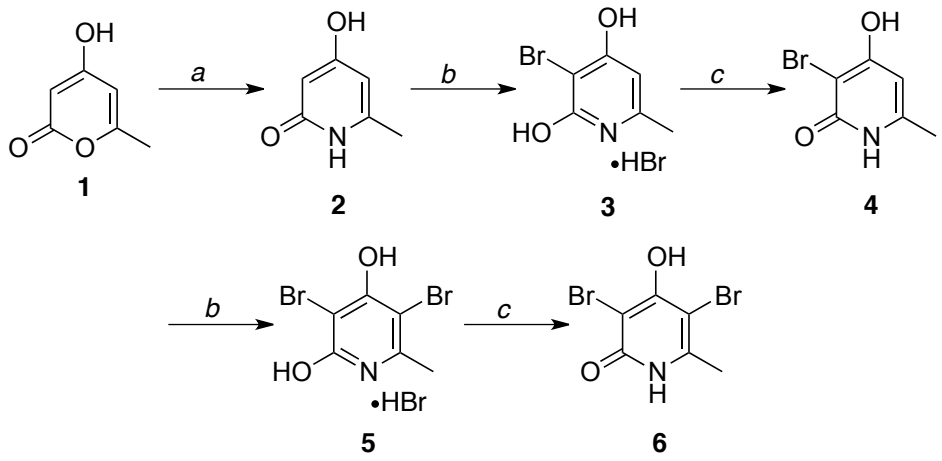


Figure 4. By introducing a chemically modified pyridone cofactor into the active site of the mono-iron hydrogenase enzyme, the catalytic properties of the enzyme will be altered, allowing them to be studied.

Results and Discussion

The easiest access point to pyridone **2** and its analogs is through pyrone **1**. As indicated by Castillo, Selness, and others, **2** and its N-substituted derivatives can be produced by amination of **1** using either an ammonia source (leading to N-H pyridones) or a primary amine (leading to N-alkyl pyridones).[9, 10, 11] With the final goal of performing various carbon coupling reactions at the 3 and/or 5 positions, the pyridone must be brominated and in some cases the hydroxyl and heteroatom groups must be protected. Various N- and O-protected, mono- and di- brominated pyridones have been synthesized. Preliminary results for CF_3 coupling have also been obtained.

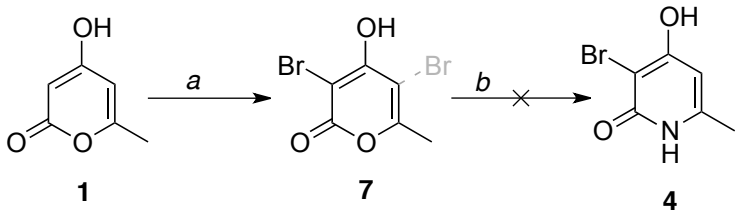
I. 4-OH Derivatives of Pyrone and Pyridone



Scheme 1. Synthesis of 3,5-dibromo-4-hydroxy-6-methylpyridone: (a) NH_4OH, reflux, 5 hr, 92%; (b) Br_2, 0 °C→RT, 70%, 79%; (c) $NaHCO_3$, reflux, THF, 33%

Pyridone **2** was produced by the amination of pyrone **1** in refluxing NH_4OH and was precipitated from the resulting green solution using concentrated aqueous sodium bisulfate.[9, 10, 11] Pyridone **2** was slurried in DCM and brominated using two equivalents of Br_2 at 0 °C. Interestingly, bromination stops at mono-bromination at the 3 position, leaving the 5 position unmodified. It was determined that an insoluble, unreactive HBr salt of monobromo-pyridone **3** was formed. To obtain dibrominated **6**, the monobrominated HBr salt **3** was neutralized in refluxing THF with a stoichiometric amount of $NaHCO_3$ to give freebase **4** which was subsequently brominated as before. The resulting dibrominated pyridone HBr salt **5** was then neutralized in identical fashion to give freebase **6**. The use of $KHCO_3$ in place of $NaHCO_3$ in the neutralization results in an unintended product which turns bright pink upon standing. It is speculated that the KBr produced in the reaction attacks the pyridone ring resulting in the pink product. The neutralization of **3** suffers from relatively low yields because it relies on the precipitation of the product **4** from THF. A work up process discovered later in the year may alleviate the problem of needing to perform a separate neutralization reaction. Namely, the DCM

bromination slurry may be poured into a vigorously stirred 5% aqueous sodium bisulfite solution to simultaneously neutralize any remaining bromine and yield the freebase.



1 **7** **4**

Scheme 2. Proposed alternate synthesis: (a) Br_2, 0 °C→RT, 98%; (b) NH_4OH, reflux or 1 M NH_3 in MeOH, 0%

An alternative route to the dibrominated pyridone was attempted in which the pyrone **1** would be initially mono- or di-brominated and then aminated to form **4** or **6** respectively. This synthetic route was unsuccessful, however. One heuristic that seems to be true for all 4-OH and 4-OMe pyrones and pyridones is that the 3 position is more susceptible to electrophilic aromatic substitution than the 5 position. In the case of **1**, the 5 position is significantly less reactive, and as a result, synthesis of the dibrominated pyrone has not been achieved. Treatment with Br_2 in DCM gave only monobrominated pyrone **7.** Even under more forcing conditions of reflux with excess Br_2, only the monobrominated pyrone **7** was obtained. Harris et al describe the use of catalytic I_2, excess Br_2, and slightly elevated temperatures (35 °C) to brominate the recalcitrant 5 position of a similar pyrone, but this method was also unsuccessful in our hands.[12] No method has been found to activate the 5 position of **1**. Furthermore, several unsuccessful attempts were made to convert the monobrominated pyrone **7** to the pyridone **4**. Amination using refluxing aqueous NH_4OH resulted in a mixture of products, and amination using a methanolic solution of ammonia was also unsuccessful.

II. Building Blocks for Biomimetic Ligands

As discussed in the Introduction and Background sections, one of the major goals of the Rose Group is to synthesize the target compound pictured in Figure 5. This ligand will be used to synthesize biomimetic dicarbonyl Fe complexes which resemble the coordination sphere of the mono-iron hydrogenase active site.

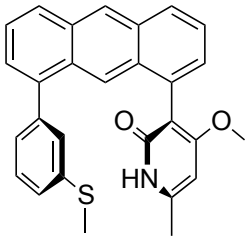
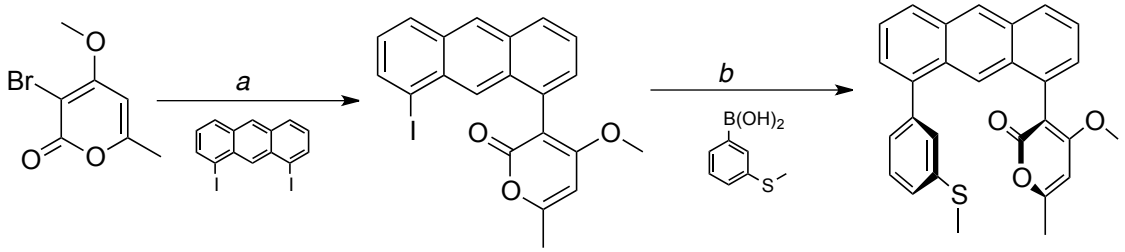


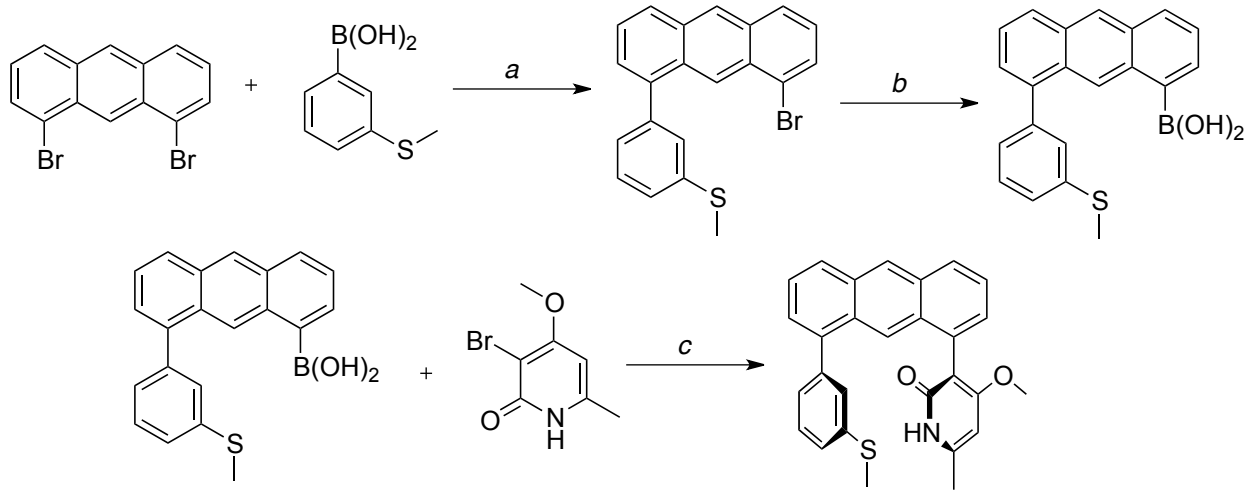
Figure 5. The target ligand is composed of an anthracene scaffold coupled with a *m*-thioether and a pyridone with a 6-methyl group that can form an acyl unit.[13]

While working toward the target compound, several test compounds were produced as models for the final target. These models contained coupling partners that would be more straightforward to work with, e.g., **8**, **12**, and **17**. These simpler systems did not contain the acidic pyridone –NH associated with coupling partner **11**, and in fact, coupling partner **8** was the simplest to work with because it is a pyrone. The common feature of each of these coupling partners is that incompatible functional groups (-OH, -NH) were blocked. Scheme 3 summarizes the process used to synthesize the model ligands using **8**, **12**, and **17** in which a Negishi coupling is followed by Suzuki coupling.



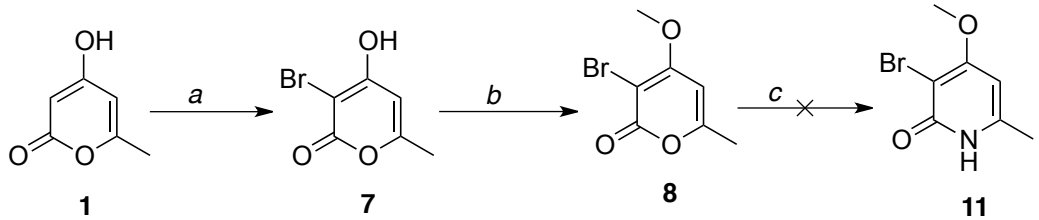
Scheme 3. Example of target ligand synthesis by Negishi coupling followed by Suzuki coupling: (a) *i*.BuLi, *ii*.$ZnCl_2$, *iii*.1,8-diiodoanthracene; *iv*.$Pd(PPh_3)_4$; (b) $Pd(PPh_3)_4$, Na_2CO_3, THF/H_2O [syntheses by Junhyeok Seo]

The target ligand was ultimately synthesized by a slightly different method than that in Scheme 3 that would not be sensitive to the pyridone –NH group in **11**, avoiding the need for a nitrogen protecting group. As summarized in Scheme 4, the thioether substituent is first asymmetrically coupled to a dibromo anthracene scaffold by a Suzuki reaction, the second bromine is then converted to a boronic acid and, finally, the unprotected pyridone **11** is coupled by a second Suzuki reaction to yield the target ligand. These syntheses will not be described in detail, but are presented to give context and highlight the motivation for the synthesis of various 3-Br coupling partners.



Scheme 4. Sequential Suzuki Coupling: (a) $Pd(PPh_3)_4$, Na_2CO_3, THF/H_2O; (b) *i*.PhLi, *ii*.$B(OEt)_3$, *iii*.HCl, THF; (c) $Pd(dba)_2$, XPhos, Na_2CO_3, $toluene/H_2O$ [syntheses by Junhyeok Seo]

A) 3-Br coupling partners

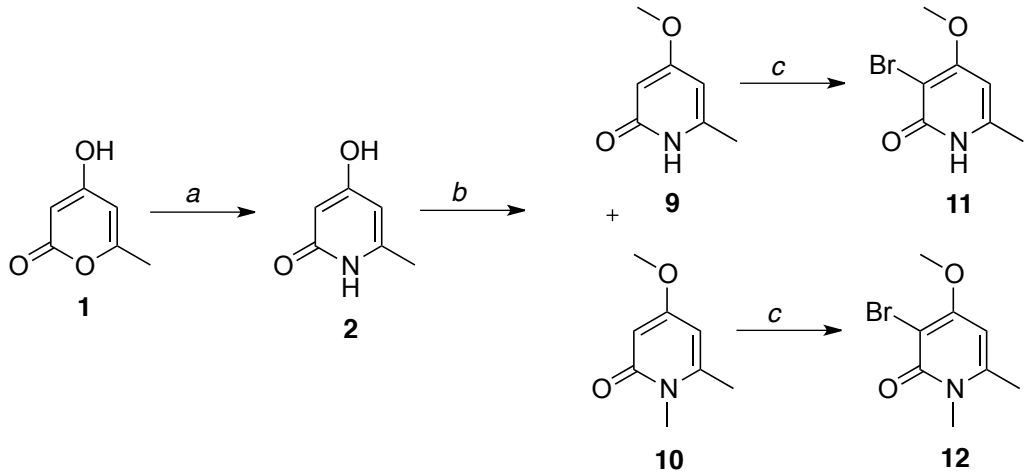


1 **7** **8** **11**

Scheme 5. (a) Br_2, 0 °C→RT, ~100%; (b) DMS, acetone, K_2CO_3, reflux, 71%; (c) NH_4OH_4, reflux, 0%

Several 3-Br, carbon-carbon coupling partners were synthesized for use in methodical work toward synthesizing an anthracene-scaffold biomimetic ligand. Several coupling techniques

were used, including Negishi and Suzuki coupling, but each of these techniques required activation of the 3 position of the coupling partner (pyrone or pyridone), protection of the 4-OH group and, optimal protection of the hetero-nitrogen (Negishi conditions). To this end, methylation of the 4-OH group of both pyrones and pyridones was explored. Methylation of 3-Br-4-OH pyrone **7** using MeI gave an intractable mixture of methylated products, indicating that a more selective methylating agent should be used. Methylation of **7** to give 3-Br-4-MeO pyrone **8** was successfully performed using dimethyl sulfate (DMS) in refluxing acetone with K_2CO_3 as the base. This substrate was successfully coupled to the anthracene scaffold by Negishi coupling as a proof of concept for the asymmetric synthesis of the anthracene ligand.



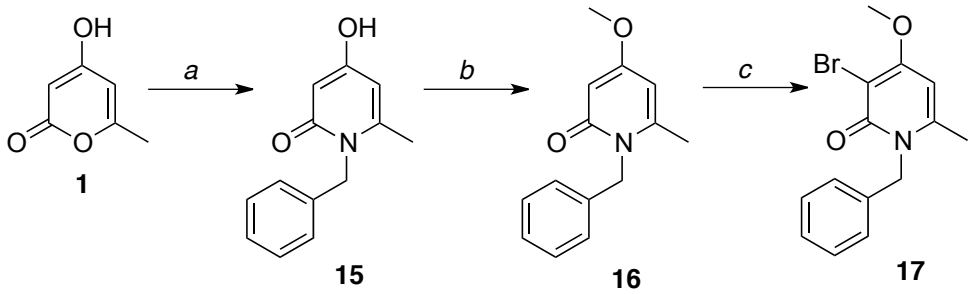
Scheme 6. (a) NH_4OH, reflux, 5 hr, 92%; (b) DMS, acetone, K_2CO_3, reflux, 36% (NH), 23% (NMe); (c) for NH: 1.0 eq Br_2, -10 °C, 92%; for NMe: 1.0 eq Br_2, -40 °C, 64%

While methylation of the brominated pyrone **7** proved straightforward, methylation of 3-Br-4-OH pyridone **4** using DMS gave a complicated mixture of methylated products. To produce 3-Br-4-MeO-NH pyridone **11**, the order of bromination and methylation was thus reversed. Methylation of **2** using DMS gave a mixture of 4-MeO-NH-pyridone **9** and 4-MeO-NMe-pyridone **10**. Using 10:1 DCM:MeOH as the eluent in TLC, a small degree of separation between the products could be obtained (**9** Rf=0.55, **10** Rf=0.65). Pure samples of **9** and **10** could

be obtained by column chromatography using the same solvent system, but the yield suffered because the elution of each product overlapped to some degree. Attempts were made to minimize the formation of the N-Me product by reducing the pH of the reaction. The use of $KHCO_3$ instead of K_2CO_3 was expected to leave the pyridone nitrogen protonated, and allow the more acidic 4-hydroxy group to be selectively deprotonated for methylation. Similar proportions of **9** and **10** were produced regardless of which base was used. After some time, it was observed that **9** and **10** had a rather large differential solubility in ethyl acetate, allowing the separation of large quantities of the two compounds: the crude reaction mixture after neutralization and solvent evaporation may be finely ground in a mortar and pestle and transferred into a conic filter paper and funnel. The -NMe pyridone **10** may be washed into the filtrate (along with a substantial quantity of –NH pyridone **9**) with multiple portions of EtOAc leaving only **9** behind as a solid. The progress of the separation is monitored by spotting successive washes on TLC until the –NMe spot is no longer present.

Both 3-Br, 4-MeO, NH pyridone **11** and 3-Br, 4-MeO, NMe pyridone **12** were synthesized for use as coupling partners in the anthracene biomimetic ligand project. The purpose of 'protecting' the nitrogen position in **12** with a methyl group was to avoid the complication caused by the presence of the acidic –NH proton when considering catalyst compatibility. Unfortunately, no literature method for removal of the methyl group was found. Just as in the case of **8**, successful coupling by Junhyeok Seo of **12** served as a proof of concept in the incremental progress toward a functional ligand. Some reaction optimization was necessary in the bromination of **9** and **10** to avoid the production of the di-bromo adducts **13** and **14**. In the case of **9**, the presence of the 4-MeO group greatly increases the pK_a of the pyridone proton. As a result, the HBr salt is not formed as a natural stopping point between the mono- and

di- bromo adducts. In the case of **10**, it is not possible for the HBr salt to form. The increased solubility of OMe-pyridones versus OH-pyridones likely also leads to greater dibromination. Fortunately, the differential reactivity of the 3 and 5 positions toward electrophilic aromatic substitution can be used to control the reaction kinetically. Dropwise addition of 1.0 equivalents of Br_2 to a DCM slurry of **9** or **10** at -10°C and immediate quenching in 5% aqueous $NaHSO_3$ gives good selectivity for the mono-bromo adducts **11** and **12** with some starting material present. In cases where the purity of **11** was important, a slight excess of Br_2 was used to push the reaction to slight dibromination. *The separation of **11** and **13** by flash column chromatography using EtOAc is much easier than separation of **9** and **11** (see synthetic procedure).* The di-bromo adducts **13** and **14** can be produced in pure form without chromatography by heating with excess bromine.

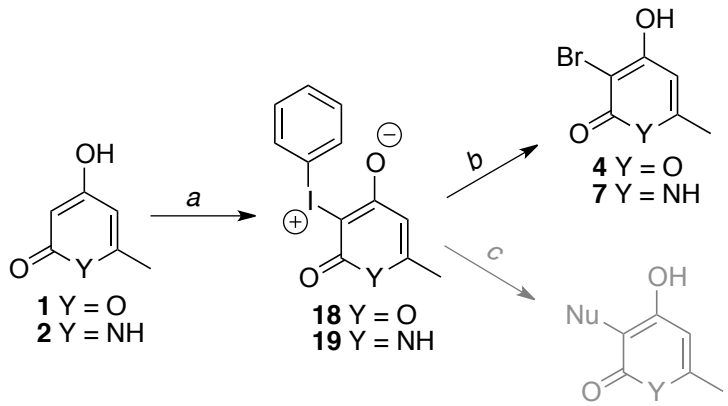


Scheme 7. (a) H_2O, $BnNH_2$, reflux, 78%; (b) DMS, acetone, K_2CO_3, reflux, 71%; (c) 1.0 eq Br_2, -40 °C, 74%

While exploring the various methods of coupling a 4-MeO pyridone derivative to anthracene, it became clear that an N-protected pyridone that could be easily deprotected would be useful. Attempts at protection with Boc_2O were not successful. Many literature sources indicated that N-alkyl pyridones could be synthesized by amination using primary alkylamines.[9, 11] Amination of **1** with benzylamine afforded an N-protected pyridone **15** that, in principle, should be deprotected by hydrogenation or other means. Methylation of **15** by DMS gave 4-

MeO, N-Bn pyridone **16** in good yield. Even after purification of **16** by flash column chromatography on silica using EtOAc as an eluent, the yellow fractions containing the product would turn green while being rotavaped or standing in air. Off-white crystals were observed to form from concentrated samples of this green solution. The green impurity was removed by recrystallization in EtOAc. After purification, **16** was brominated using 1.0 equivalents of Br_2 at -40°C to give **17** which was coupled to 1,8 diiodoanthracene by Negishi coupling as in Scheme 3.

B) Miscellaneous Coupling Partners



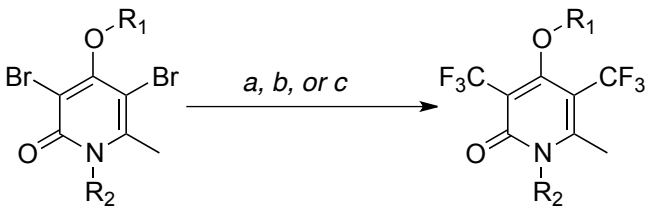
Scheme 8. Y=O: (a) 0.1 M Na_2CO_3, diacetoxy(iodobenzene), gentle heating, 72%; (b) HBr, EtOH, 70 °C, 5 min, 50%; **Y=NH**: (a) 0.1 M Na_2CO_3, diacetoxy(iodobenzene), gentle heating, <20% yield; (b) HBr, EtOH, 70 °C, 5 min

One additional reaction of pyrones and pyridones is the formation of an iodonium ylide when exposed to hypervalent iodine reagents in a slightly basic solution.[14] The phenyl iodonium ylides of both **1** and **2** were produced by *gently* heating with diacetoxy(iodobenzene) in an aqueous solution of 0.1 M Na_2CO_3. As soon as all the reactants have been dissolved, the mixture must be removed from the heat, allowing the precipitation of the 3-iodonium ylide. Excess heating results in thermal decomposition of the ylide to form 3-iodo 4-phenoxy compounds. A crystal structure of 3-iodo-4-phenoxypyridone can be seen in the Experimental section. The

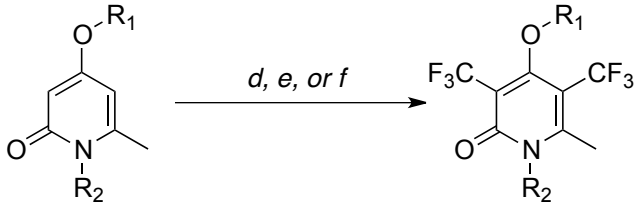
utility of ylides **18** and **19** lies in their reactivity toward weak nucleophiles. To confirm the identity of the ylides, they were refluxed in EtOH with HBr for 5 minutes, resulting in the 3-bromo adducts **3** and **7**. In principle, these ylides could be reacted with more interesting nucleophiles than Br^-—like anthracene derivatives or CF_3^- sources.

III. Trifluoromethylation of Pyridones for Synthetic Mutations

While they were not applicable in the ligand coupling reactions discussed in previous sections, the purpose in synthesizing the di-bromo pyridones, **13** and **14**, was their utility as activated coupling partners in the synthesis of 3,5-bis-CF_3 pyridones. The incorporation of a trifluoromethyl (CF_3) group into an organic molecule can greatly influence a number of properties, including lipophilicity, steric size, and pK_a values. As an electron-withdrawing group, even one trifluoromethyl group will strongly alter the electronics of a compound; two CF_3 groups will have an even more profound effect. Despite a great deal of research attention in the past twenty years, the formation of CF_3-arene bonds still remains difficult. Many of the known methods for CF_3 coupling employ harsh reagents and conditions, leading to narrow applicability. Pyridone compounds, like other nitrogen heterocycles, are prone to decomposition, so their trifluoromethylated derivatives have been inaccessible until recently. New research has led to the development of several Pd and Cu catalyzed trifluoromethylations employing relatively mild conditions.[15, 16, 17] A number of metal-free trifluoromethylations have also been discovered, including a notable radical reaction discovered by Baran and coworkers.[18, 19, 20] Because neither the target compound **22** nor any similar compound have been reported in the literature, several methods of coupling CF_3 groups to heterocycles were selected from the literature as potential candidates for a screen of reaction conditions which might yield the desired product.



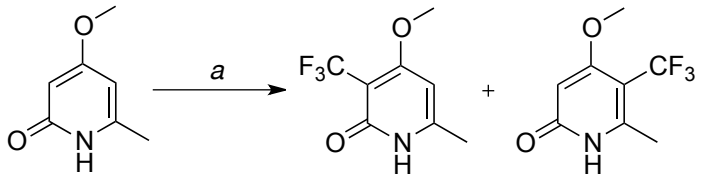
Scheme 9. Reactions requiring activation by bromination: **R_1=H, Me; R_2=H, Me, Bn.** (a) $Pd(dba)_2$, BrettPhos/RuPhos (1.5×cat), $TESCF_3$ (4 eq.), KF/CsF (4 eq.), dioxane, 120 °C, 20 hrs; (b) $Cu(phen)(CF_3)$, DMF, RT→50 °C; (c) CuI (2 eq.), $FO_2SCF_3CO_2Me$ (4 eq.)



Scheme 10. Reactions that do not require activation**: R_1=H, Me; R_2=H, Me, Bn.** (d) $AgF/AgCO_3$, $PhI(OAc)_2$, $TESCF_3$, DMSO, RT in air; (e) $PhI(Oac)_2$ (1.2 eq.), $TESCF_3$ (2.4 eq), K_3PO_4 (2.4 eq.) MeCN, 85 °C, 6 hrs; (f) $NaSO_2CF_3$ (3 eq.), tBuOOH (5 eq.), DCM:H_2O 2.5:1 ratio, RT in air

Reactions **A-F** (Schemes 9 and 10) describe literature methods for coupling a CF_3 group to a nitrogen heterocycle. Reactions **A-C** (Scheme 9) posses some similarities. Each of these reactions depends upon a metal catalyst, either Pd or Cu, in conjunction with an anionic CF_3^- group. In each of these reactions the substrate is activated by bromination prior to coupling. The metals in these reactions mediate the replacement of the Br^- ions with CF_3 groups. In reaction **A**, palladium catalyzes CF_3 coupling by a classical Pd(0)/Pd(II) mechanism.[15] In reaction **B**, the commercially available Cu-CF_3 reagent, 'Trifluoromethylator', reacts with Br activated heteroarenes.[16] In reaction **C**, methyl fluorosulfonyldifluoroacetate decomposes to produce a CF_3^- group in the presence of CuI, leading to the formation of an *in situ* $CuCF_3$ reagent.[17] Reactions **D-F** (Scheme 10) proceed through different mechanisms than **A-C** which do not require pre-activation by bromination. Reactions **D** and **E** involve the use of diacetoxyiodobenzene as an oxidant and $TESCF_3$ as a CF_3^- source.[18, 19] In contrast with all of the

other reactions pictured, reaction **F** proceeds by forming CF_3• radicals that attack the unactivated C-H carbons by a radical mechanism.[20]

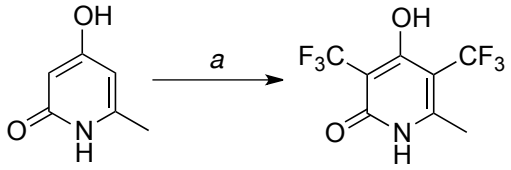


9 **20** **21**

Scheme 11. Baran's radical trifluoromethylation gives a mixture of regioisomers when applied to **9**: (a) $NaSO_2CF_3$ (3 eq.), tBuOOH (5 eq.), DCM:H_2O 2.5:1 ratio, RT in air

Ironically, after purchasing the majority of the chemicals needed for screening all proposed reactions, one of the first reactions performed was successful. Reaction **F**, the radical trifluoromethylation developed in the Baran Lab, was particularly attractive because the reaction was performed without the need for air-free conditions—even using water as one of the solvents. Notably, the reaction has been performed on chemicals similar to pyridones. For example, the radical trifluoromethylation of both uridine and deoxyuridine under Baran's conditions was reported by Ji et al. In fact, each of the nucleosides has been trifluoromethylated by this method.[21] To test the reaction, radical trifuoromethylation was performed using 4-methoxy-NH pyridone **9** as the substrate. Following workup with $NaHCO_3$ and DCM extraction, ^{19}F NMR indicated the presence of fluorine in the product, and the addition of one CF_3 group was confirmed by mass spectrometry (ESI-MS-see appendix). The regioselectivity of the reaction was ambiguous, however. It was difficult to determine whether compound **20** or **21** had been synthesized. This issue was resolved by close inspection of the ^1H NMR spectrum. The ^1H-^{19}F nuclear spin coupling of the 6-methyl protons with the adjacent 5-CF_3 group (as in **21**) resulted in a characteristic quartet caused by CF_3 splitting. However, a singlet methyl peak was also observed. This data, combined with the integrations of these peaks indicated that both

regioisomers were present, with **20** present in greater proportion (1:0.1**)**. The quartet was echoed by a second, smaller quartet farther downfield. This trace signal is speculated to be the di-CF_3 adduct. Several literature references indicated that a greater proportion of di-substituted products was observed when the more forcing conditions of heating to 50°C and multiple reagent addition were applied. With the goal of producing predominately di-substituted 4-methoxy pyridone, these conditions were tested, but the resulting mixture of products resembled the product profile obtained from the previous reaction at room temperature.



2 **22**

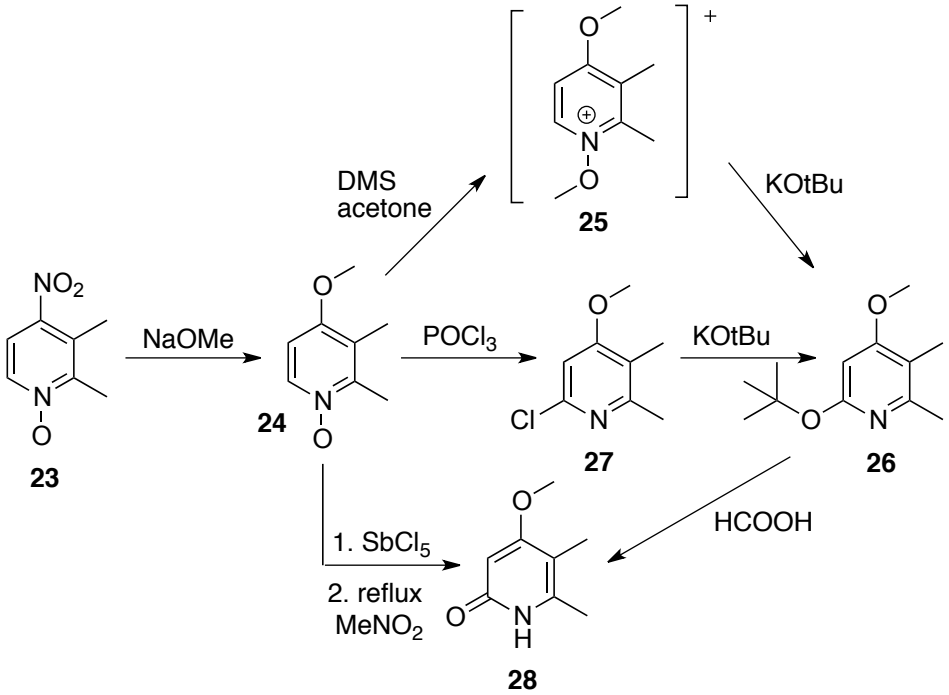
Scheme 12. Radical trifluoromethylation applied to pyridone **2**: (a) $NaSO_2CF_3$ (3 eq.), tBuOOH (5 eq.), DCM:H_2O 2.5:1 ratio, RT in air

Remarkably, the desired bis-CF_3 pyridone framework was obtained from an even simpler starting material. Reaction of the unprotected compound **2** under the mild Baran conditions stated above yielded compound **22**. This success indicates that the trifluoromethylation procedure is surprisingly tolerant of protic groups, even heteroaryl hydroxy groups.

IV. Proposed Synthesis of 5-Me Pyridone

Currently metallation procedures are underway (J. Seo) using the target ligand from the previous section (Figure 5). These procedures have brought to light the possibility that the C5 position of the current coupling partner **11** is subject to electrophilic attack. To remedy this instability, the synthesis of 5-methyl pyridone **28** is proposed. Compound **28** can be easily brominated at C3 to yield an improved coupling partner. Several attempts were made by other

members of the group to synthesize the 4-OH precursor to **28** by various pyrone and pyridone cyclizations without success. An alternative synthesis by modification of the pre-formed pyridine ring starts from the commercially available compound **23**. Nucleophilic substitution in MeOH using excess sodium methoxide gives the 4-OMe compound **24**.[22, 23] From compound **24** several synthetic routes are possible. Most simply, intermolecular oxygen transfer promoted by $SbCl_5$ could be performed.[24] Alternatively, chlorination of **24** at C2 by reflux in $POCl_3$ and subsequent nucleophilic substitution using potassium *tert*-butoxide could result in the introduction of the desired oxygen-carbon bond, giving **26**.[25] Birkholz et al report the facile cleavage of this *tert*-butyl ether at room temperature in formic acid.[26] One other putative method involves the enhancement of the electrophilicity of C2 by methylation of the N-oxide moiety of **24** to give methylsulfate salt **25**. Subsequent reaction with potassium *tert*-butoxide is hypothesized to afford **26** by an alternate method.



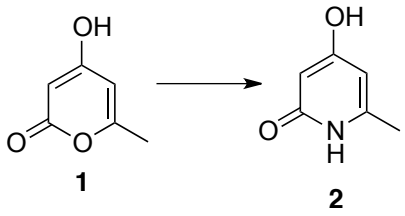
Scheme 13. Starting from commercially available compound **23** it is theoretically possible to synthesize 5-methyl pyridone **28** in a few alternate steps.

Conclusion

In summary, the Rose Group has designed and set out to synthesize a biomimetic ligand with an anthracene backbone modeled after the coordination geometry of the mono-iron hydrogenase active site. Fe and Co metallations using this ligand to produce biomimetic carbonyl complexes are ongoing. Several pyrone and pyridone coupling partners described herein were synthesized to aid in the synthesis of this ligand. Future work will include the synthesis of 5-methyl pyridone **28** to prevent oxidation/electrophilic addition at the C5 position in subsequent generations of pyridone ligands.

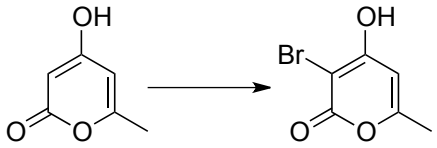
Experimental

Syntheses



4-hydroxy-6-methyl-pyridone (2)

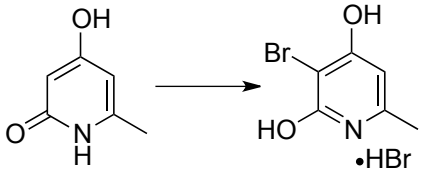
This procedure and the synthesis of this compound are described in a number of literature sources.[9, 10, 11] Pyrone **1** (10 g, 79.3 mmol) was added to an excess of aqueous ammonium hydroxide (55 mL, 400 mmol) in a 150 mL round bottom flask. The mixture was refluxed for 6 hours. In some cases, after refluxing, a white precipitate is present with a yellow supernatant. More often, however, no precipitate will form, and the entire solution is deep green. This is likely the result of complex formation with a trace-metal impurity under basic conditions. Product **2** was precipitated by reducing the pH to 4-6 using saturated aqueous sodium bisulfate ($NaHSO_4$). The precipitate was collected by vacuum filtration, washed with cold water, and dried at 50 °C overnight, affording 9.14 g of gray powder (92% yield). ^{1}H NMR in d^6-dmso (δ in ppm from TMS): 2.06 s (3H), 5.31 d (1H), 5.57 d (1H), 10.33 s (1H) 10.93 s (1H). Selected IR bands (ν in cm^{-1}): 1635 s, 1598 s, 1447 m, 1349 m, 1262 m, 1231 s, 1171 m, 897 m, 841 m, 829 s, 627 m, 595 m, 534 s, 512 m, 407 s.



1 **7**

3-bromo-4-hydroxy-6-methyl-pyrone (7)

Pyrone **1** (1.5 g, 11.9 mmol) was slurried in ~40 mL of CH_2Cl_2 in a 100 mL round bottom flask and allowed to cool in a 0 °C ice bath. A solution of Br_2 (0.62 mL, 12 mmol) in ~3 mL of CH_2Cl_2 was added dropwise to this slurry over the course of 10 minutes. The slurry changed color from beige to yellow and then to orange/brown. The mixture was allowed to come to room temperature over the course of about 30 minutes. The white precipitate was collected by gravity filtration and washed with CH_2Cl_2 until the washes became clear. The final mass of the product was 2.4 g (98% yield). ^{1}H NMR in d^6-dmso (δ in ppm from TMS): 2.17 s (3H), 6.10 s (1H), 12.5 s (1H). Selected IR bands (ν in cm^{-1}): 1670 s, 1624 s, 1552 m, 1440 m, 1407 s, 1396 s, 1378 s, 1233 w, 1029 s, 951 s, 816 s, 749 s, 634 m, 625 m, 612 s, 421 s.

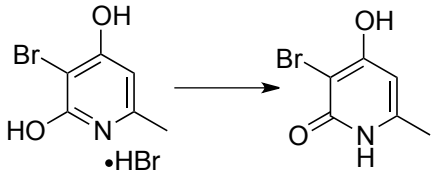


2 **3**

3-bromo-4-hydroxy-6-methylpyridone (HBr Salt) (3)

Pyridone **2** (0.63 g, 5 mmol) was slurried in ~60 mL of CH_2Cl_2 in a 100 mL round bottom flask and allowed to cool to 0 °C. A solution of Br_2 (0.26 mL, 5 mmol) in ~3 mL of CH_2Cl_2 was added dropwise to this slurry over the course of 10 minutes. The slurry changed color from beige to yellow and then to orange brown, and an intermediate compound formed as an amorphous solid at the bottom of the flask. The mixture was allowed to come to room temperature over the course

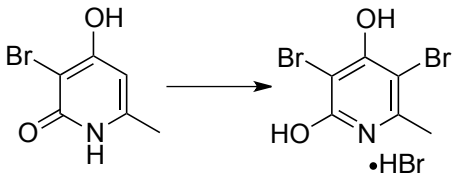
of about 30 minutes. The light brown precipitate was collected by gravity filtration and washed with CH_2Cl_2 until the washes became clear. The final mass of the product was 0.99 g (70% yield). ^{1}H NMR in d^6-dmso (δ in ppm from TMS): 2.07 s (3H), 5.79 s (1H), 11.1 s (1H) 11.4 s (1H). Selected IR bands (ν in cm^{-1}): 3038 br, 2932 m, 1615 s, 1470 w, 1338 w, 1210 m, 1189 m, 1059 w, 824 m.



3 **4**

3-bromo-4-hydroxy-6-methylpyridone (Freebase) (4)

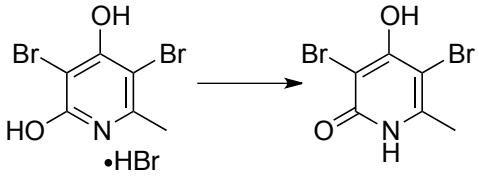
The HBr salt **3** (1.36 g, 4.8 mmol) was suspended in ~75 mL of THF. To this suspension was added 4.8 mmol of $NaHCO_3$. The mixture was stirred for 10 minutes at room temperature and for 10 more minutes at reflux. After cooling to room temperature, the clear beige solution was placed in the refrigerator overnight. In the morning, beige solids had precipitated out of an orange solution. The solids were collected by vacuum filtration and washed with water. The product was dried in a 50 °C oven over P_2O_5, giving 0.33 g of beige powder (33% yield). ^{1}H NMR in d^6-dmso (δ in ppm from TMS): 2.07 s (3H), 5.78 s (1H), 11.13 s (1H) 11.42 s (1H). Selected IR bands (ν in cm^{-1}): 1625 s, 1596 m, 1564 m, 1460 m, 1382 m, 1346 s, 1044 m, 799 m.



4 **5**

3,5-dibromo-4-hydroxy-6-methylpyridone (HBr Salt) (5)

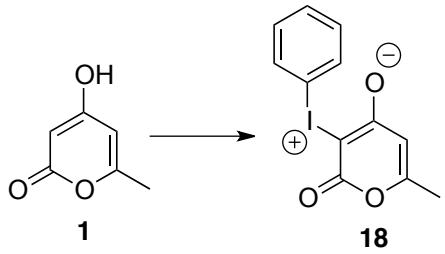
A Br_2 solution (0.05 mL, 1 mmol) in DCM was added dropwise to a stirred suspension of **4** (175 mg**,** 0.86 mmol) in DCM over the course of about 10 minutes at 0 °C. The color of the suspension changed from cloudy white to yellow and finally to orange. A brown amorphous lump formed at the bottom of the flask. The reaction was allowed to come to room temperature and stirred overnight, resulting in a fine white precipitate the next morning. The precipitate was isolated by gravity filtration and washed repeatedly with DCM until the filtrate was no longer brown. The mass of the white compound was 0.246 g (79% yield). ^{1}H NMR in d^6-dmso (δ in ppm from TMS): 2.25 s (3H). Selected IR bands (ν in cm^{-1}): 1597 vs, 1420 s, 1384 s, 1163 s, 1041 m, 697 m, 630 m.



5 **6**

3,5-dibromo-4-hydroxy-6-methylpyridone (Freebase) (6)

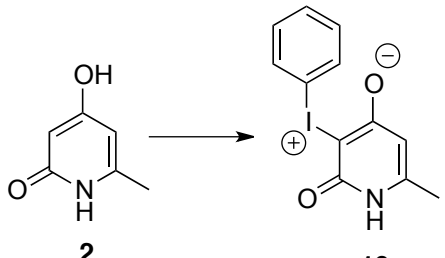
Theoretically, the HBr salt **5** could be neutralized to yield the freebase in a manner similar to the neutralization of compound **3**. However, this has not been experimentally confirmed.



1 18

6-methyl-2-oxo-3-(phenyliodonio)-pyranolate (18)

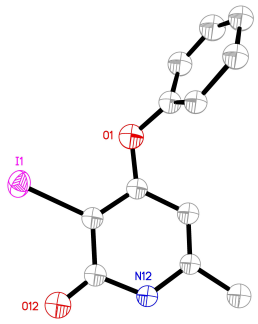
The synthesis of this compound may be found in Kappe et al. *Z. Naturforsch*. **1983**, *38b*, 398-403. Pyrone **1** (0.6 g, 4.8 mmol) was dissolved in 40 mL of an aqueous 0.1 M Na_2CO_3 solution in a 100 mL round bottom flask. To this solution was added 1.533 g (4.8 mmol) of diacetoxy(iodo)benzene, and the mixture was *gently* heated until all solids had dissolved. During this time the yellow solution quickly turned brown. The round bottom flask was placed on ice, causing the product to quickly precipitate out in small gray crystalline flakes. The product was collected by vacuum filtration and washed will a small amount of cold water, affording 1.12 g of gray crystals (72% yield). ^{1}H NMR in d^6-dmso (δ in ppm from TMS): 2.05 s (3H), 5.64 s (1H), 7.41 t (2H), 7.52 t (1H), 7.76 d (2H). Selected IR bands (ν in cm^{-1}): 1659 m, 1518 s, 1487 m, 1468 m, 1397 m, 1368 m, 1304 m, 991 s, 982 s, 831 m, 743 m, 731 s, 678 m, 649 m, 586 m, 562 m, 501 m, 447 m, 426 m.



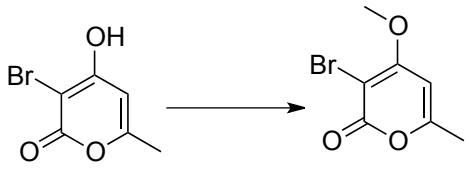
2 19

6-methyl-2-oxo-3-(phenyliodonio)-pyridonolate (19)

Pyridone iodonium ylide **19** was synthesized in a manner almost identical to that of pyrone ylide **18**. Pyridone **2** was gently heated in a 0.1 M Na_2CO_3 solution in the presence of diacetoxy(iodo)benzene. White flakes of the desired product precipitated from the solution within 30 minutes. The ^{1}H NMR spectrum in d^6-dmso (δ in ppm from TMS) of the products that may be the ylide contains the following peaks: 1.96 s (3H), 5.32 s (1H), 7.39 t (2H), 7.48 t (1H), 7.74 d (2H), 10.1 s (1H). Selected IR bands (ν in cm^{-1}): 1599 m, 1478 m, 1468 m, 733 s, 624 m, 582 m, 522 s, 446 m.



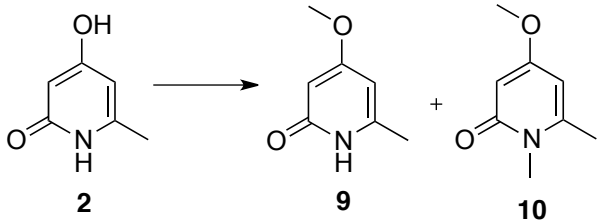
The iodonium ylides are prone to thermal decomposition to form 3-iodo-phenoxy compounds. Successful synthesis of the ylide was confirmed by nucleophillic substitution of Br^- by reaction with HBr in ethanol. The most distinguishing characteristic of the iodonium ylide vs the 3-iodo-phenoxy compound spectra is that the doublet is the most downfield (larger ppm) peak for the ylides. The proton at C5 is also shifted upfield by about 0.2 ppm. The discernable ^{1}H NMR shifts for the phenoxy pyrone in d^6-dmso (δ in ppm from TMS) are 2.14 s (3H), 5.80 s (1H), 7.20 d (2H) with two triplets between 7.4 and 7.6. The discernable ^{1}H NMR shifts for the phenoxy pyridone in d^6-dmso (δ in ppm from TMS) are 2.07 s (3H), 5.49 s (1H), 7.09 d (2H), 7.25 t (1H), 7.44 t (2H), 11.8 s (1H). Selected IR bands (ν in cm^{-1}): 1628 s, 1586 s, 1486 m, 1452 m, 1318 m, 1246 s, 1198 s, 1010 m, 1001 m, 778 m, 771 m, 698 s, 555 s, 477 s.



7 **8**

3-bromo-4-methoxy-6-methyl-pyrone (8)

Pyrone **7 (**3.5 g, 17 mmol) was slurried with ~80 mL of acetone in a 150 mL round bottom flask. An excess of K_2CO_3 (6 g, 0.43 mmol) was added to the mixture and the reaction was stirred for 10 minutes. Dimethyl sulfate (2 mL, 21 mmol) was added to the flask in a dropwise fashion over the span of 10 minutes. The reaction was then heated to reflux for 3 hours, at which point the cloudy suspension had become clear yellow with a great deal of undissolved base at the bottom. The reaction mixture was poured in to a beaker containing about 80 mL of saturated aqueous NH_4Cl. The organic materials were extracted using 3×30 mL of EtOAc, and these extracts were combined and dried over Na_2SO_4. The solvent was removed by rotary evaporation to yield 2.64 g of the desired product (70.5% yield). ^{1}H NMR in d^6-acetone (δ in ppm from TMS): 2.28 s (3H), 4.04 s (3H), 6.52 s (1H). Selected IR bands (ν in cm^{-1}): 1703 s, 1640 s, 1526 s, 1317 s, 1208 m, 1000 m, 902 s, 841 m, 741 s.



2 **9** **10**

4-methoxy-6-methylpyridone and 4-methoxy-1,6-dimethylpyridone (9 and 10)

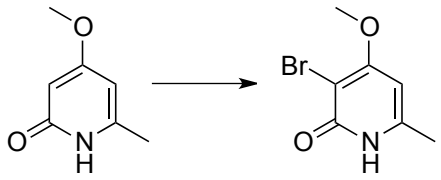
Two methylated derivatives of **2** were synthesized concurrently and subsequently separated by solubility and column chromatography. Pyridone **2** (6.6 g, 52.8 mmol) was slurried in a 150 mL

round bottom flask in ~120 mL of acetone. To this mixture was added 2 equivalents (15.32 g, 111 mmol) of K_2CO_3. After a few minutes, 1.0 equivalents of dimethyl sulfate (5.0 mL, 52.8 mmol) were added, and the reaction was refluxed for 3 hours. This reaction mixture was poured into a beaker containing ~50 mL of stirred concentrated aqueous NH_4Cl. The organic products were extracted using 3×30 mL of DCM. The DCM layers were dried over sodium sulfate and the solvent was removed by rotary evaporation. The resulting solid product appeared to consist of white crystals surrounded by a brown material. The solid was pulverized and rinsed thoroughly with EtOAc to remove **10** from the less soluble **9**. The remaining 2.7 g of solids consisted of pure **9** by NMR **(**36% yield). ^{1}H NMR in $CDCl_3$ (δ in ppm from TMS): 2.27 s (3H), 3.73 s (3H), 5.73 s (2H), 12.8 s (1H). Selected IR bands (ν in cm^{-1}): 1640 vs, 1446 s, 1226 vs, 1155 s, 1055 s, 894 m, 809 vs, 792 vs, 528 vs, 547 s, 429 m.

The filtrate, which contained more concentrated **10** was dried by rotary evaporation, dissolved in DCM, and purified on a silica gel column (eluent 10:1 DCM:MeOH) to give **10** (23% yield). ^{1}H NMR in $CDCl_3$ (δ in ppm from TMS): 2.27 s (3H), 3.43 s (3H), 3.71 s (3H), 5.74 s (1H), 5.81 s (1H). Selected IR bands (ν in cm^{-1}): 1651 m, 1587 s, 1561 s, 1413 m, 1358 m, 1243 m, 1216 m, 1136 m, 923 m, 857 s, 809 s.

Note:

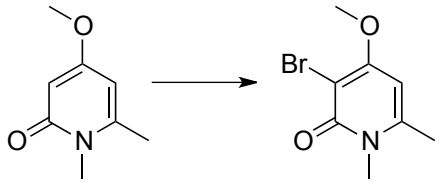
Compound **10** can be made in high yield by performing the above reaction with 2.0 equivalents of dimethyl sulfate. Flash column chromatography on silica using 10:1 DCM:MeOH as the eluent can be used to purify the product.



9 **11**

3-bromo-4-methoxy-6-methylpyridone (11)

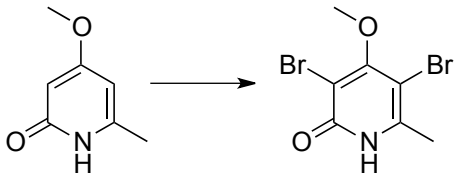
In a 100 mL round bottom flask, **9** (245 mg, 1.76 mmol) was dissolved in ~50 mL of DCM. This solution was cooled to -10 °C in a salt/ice bath. A diluted solution of Br_2 *in slight excess* (0.10 mL, 1.9 mmol moles) in DCM was added dropwise over 10 minutes. The equivalency point is readily observed because the yellow mixture will begin to turn orange-brown. A 5% solution of $NaHSO_3$ was prepared in a 250 mL beaker. While the reaction mixture was still at -10 °C, it was poured into the neutralizing $NaHSO_3$ solution and stirred vigorously. The brown mixture became cloudy and white within about a minute. The organic products were extracted with 3x30 mL of DCM, and this solvent was dried over Na_2SO_4. The solvent was removed by rotary evaporation and analyzed by ^{1}H NMR to reveal that a small portion of the material was the dibromo species **13**. *Compound **11** is easily purified by flash column chromatography, beginning with EtOAc as the eluent to elute all **13** and switching to 10:1 $CHCl_3$:MeOH to elute **11**.* The solvent was removed, affording 354 mg of the product (92% yield). ^{1}H NMR in $CDCl_3$ (δ in ppm from TMS): 2.39 s (3H), 3.92 s (3H), 5.92 s (1H), 13.0 s (1H). Selected IR bands (ν in cm^{-1}): 1617 vs, 1450 s, 1324 s, 1266 s, 1117 s, 1035 s, 930 s, 798 s, 753 m, 626 s, 522 vs, 408 m.



10 **12**

3-bromo-4-methoxy-1,6-dimethylpyridone (12)

N-methylated **10** (410 mg, 2.7 mmol) was dissolved in ~50 mL of DCM in a 100 mL round bottom flask. This solution was cooled to -40 °C in a dry ice/acetonitrile bath, resulting in the precipitation of much of the pyridone. A diluted solution of Br_2 (0.14 mL, 2.7 mmol) in DCM was added dropwise over 10 minutes. A 5% solution of $NaHSO_3$ was prepared in a 100 mL beaker. The reaction was filtered cold and rinsed with DCM until the filtrate was clear. The solids were transferred to the beaker of $NaHSO_3$ solution where they dissolved readily. The solution was extracted with 3×30 mL of DCM and the organic extracts were combined and dried over Na_2SO_4. The solvent was removed by rotary evaporation yielding a 400 mg of NMR-pure product (64% yield). ^1H NMR in $CDCl_3$ (δ in ppm from TMS): 2.35 s (3H), 3.54 s (3H), 3.89 s (3H), 5.91 s (1H). Selected IR bands (ν in cm^{-1}): 2920 m, 2851 w, 1633 s, 1592 s, 1477 m, 1448 s, 1393 m, 1344 s, 1237 s, 1207 m, 1177 s, 1144 s, 1068 m, 1033 m, 822 s, 749 s, 626 s, 470 s.

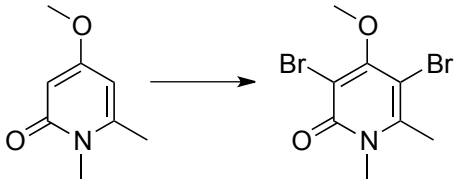


9 **13**

3,5-dibromo-4-methoxy-6-methylpyridone (13)

A Br_2 solution (0.1 mL, 1.9 mmol in DCM was added dropwise to a stirred suspension of **9** (100 mg**,** 0.7 mmol) in DCM over the course of about 10 minutes at 0 °C. The color of the solution

changed from cloudy white to yellow and finally to orange. The reaction was allowed to come to room temperature and then refluxed for a day until all the precipitate was dissolved. The solution was cooled on ice to cause the mono-brominated **11** to precipitate. The precipitate was removed by filtration and the filtrate was neutralized using 5% $NaHSO_3$. The product was extracted with 3x30 mL of DCM. The organic extracts were combined, dried over Na_2SO_4, and evaporated under reduced pressure, giving 105 mg of the desired product (51% yield). ^1H NMR in $CDCl_3$ (δ in ppm from TMS): 2.49 s (3H), 3.95 s (3H). The NH peak was notably absent, perhaps because the electron withdrawing Br groups shifted its position downfield beyond the 14 ppm range the instrument had been programmed to measure. Selected IR bands (ν in cm^{-1}): 1639 s, 1597 s, 1439 m, 1362 m, 1230 m, 1104 m, 1035 s, 923 s, 798 m, 756 w, 696 s, 646 w, 624 s, 586 w, 529 s, 419 m.

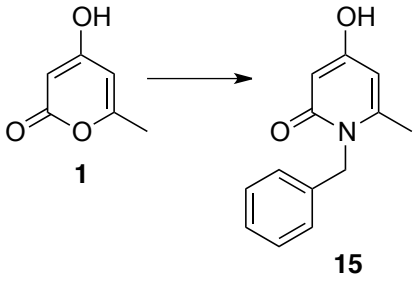


10 **14**

3,5-dibromo-4-methoxy-1,6-dimethylpyridone (14)

A Br_2 solution (0.2 mL, 3.9 mmol) in DCM was added dropwise to a stirred solution of **10** (200 mg, 1.3 mmol) in DCM over the course of about 10 minutes at 0 °C. The color of the solution changed from clear to yellow and finally to orange. As one equivalent of bromine was reached, a precipitate began to form. Eventually, 3 equivalents of bromine had been added. The reaction was allowed to come to room temperature and then was refluxed until all of the precipitate had dissolved. The mixture was poured into about 20 mL of 5% $NaHSO_3$ to neutralize the excess Br_2. The product was extracted with 3×15 mL of DCM. The organic layers were combined, dried

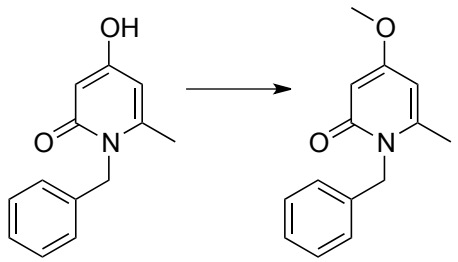
over sodium sulfate, and evaporated under reduced pressure to give 375 mg of yellow crystalline product (91.9% yield). ^{1}H NMR in $CDCl_3$ (δ in ppm from TMS): 2.56 s (3H), 3.64 s (3H), 3.91 s (3H). Selected IR bands (ν in cm^{-1}): 1646 s, 1576 m, 1511 w, 1329 w, 1156 s, 1066 m, 981 m, 945 s, 753 m, 703 s, 460 s.



1 **15**

1-benzyl-4-hydroxy-6-methylpyridone (15)

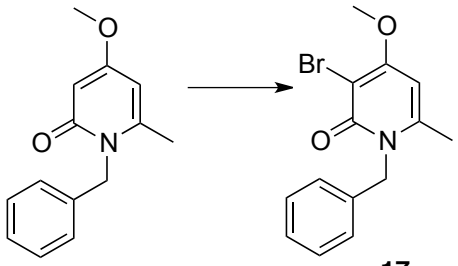
This procedure and the synthesis of this compound are described in Castillo, S. et al. *Bull. Soc. Chim. France*. **1982**, 257-261. Pyrone **1** (3.5 g, 28 mmol) was suspended in ~300 mL of water in a 500 mL roundbottom flask. The cloudy suspension became clear yellow about 10 minutes after 3.25 mL (29 mmol) of benzylamine was added. The reaction was refluxed overnight, resulting in a greenish precipitate. The product was collected by vacuum filtration and washed with 2:1 EtOH:water. The product was allowed to air dry for one day and then dried further in a 50 °C oven over P_2O_5, resulting in 4.68 g of fine brown powder (78% yield). ^{1}H NMR in d^6-dmso (δ in ppm from TMS): 2.15 s (3H), 5.17 s (2H), 5.58 d (1H), 5.78 d (1H), 7.07 d (2H), 7.23 t (1H), 7.31 m (2H). Selected IR bands (ν in cm^{-1}): 1510 s, 1452 m, 1315 s, 1231 s, 1210 s, 1179 m, 1156 m, 832 s, 733 s, 695 s, 655 m, 640 m, 597 s, 528 m, 448 s, 419 s.



15 16

1-benzyl-4-methoxy-6-methylpyridone (16)

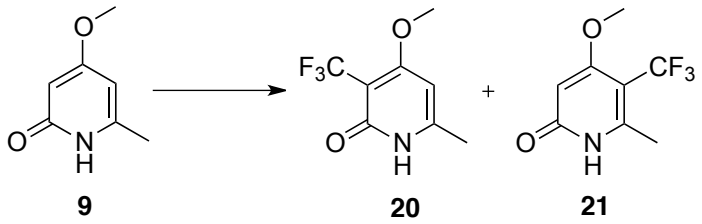
Benzyl protected pyridone **15** (1.5 g, 7 mmol) was suspended in ~50 mL of acetone in a 100 mL round bottom flask. To this suspension, K_2CO_3 (2 g, 14.5 mmol) was added. After a few minutes of stirring, dimethyl sulfate (0.66 mL, 7 mmol) was added and the reaction was heated to 80 °C for 3 hours. This reaction mixture was poured into about 30 mL of stirred concentrated aqueous NH_4Cl. The organic products were extracted using 3×20 mL of EtOAc, and this organic portion was dried over sodium sulfate and reduced to a small volume by rotary evaporation. The crude product was purified by silica column chromatography using EtOAc as the eluent. The pale yellow fractions containing the product turned green upon exposure to air, especially during rotary evaporation. The green impurity was removed by recrystallizing the product from EtOAc, affording 1.13 g of pale yellow crystals (70.7% yield). ^{1}H NMR in $CDCl_3$ (δ in ppm from TMS): 2.20 s (3H), 3.77 s (3H) 5.30 s (2H), 5.77 d (1H), 5.91 d (1H), 7.13 d (2H), 7.24 t (1H), 7.29 t (2H). Selected IR bands (ν in cm^{-1}): 1657 s, 1591 s, 1559 s, 1454 m, 1388 m, 1245 s, 1153 m, 1145 m, 1037 m, 863 m, 813 m, 730 s, 696 m, 550 m, 445 m.



16 17

1-benzyl-3-bromo-4-methoxy-6-methylpyridone (17)

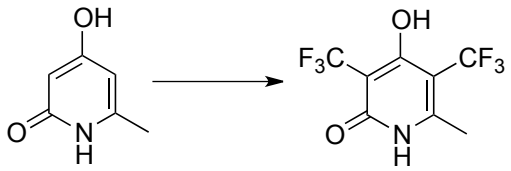
Methylated benzyl pyridone **16** (1.13 g, 4.9 mmol) was dissolved in ~40 mL of DCM and cooled to -40 °C in a dry ice/acetonitrile bath. A solution containing 1.0 eq of Br_2 (0.25 mL, 4.9 mmol) in DCM was added dropwise with stirring over the course of about 10 minutes. The cold reaction mixture was poured in to about 30 mL of a 5% $NaHSO_3$ solution in a beaker and stirred until both phases were clear and all brown color had dissipated. The product was extracted with 3×15 mL EtOAc leaving a beige organic component and clear aqueous layer. The organic extract was dried with Na_2SO_4 and reduced to a small volume by rotary evaporation. A silica TLC of this crude product using EtOAc as the eluent revealed the presence of some starting material and dibrominated pyridone in addition to the desired product. Compound **17** was purified by flash column chromatography on silica using EtOAc as the eluent affording 1.12 g of the desired product (74% yield). ^{1}H NMR in $CDCl_3$ (δ in ppm from TMS): 2.28 s (3H), 3.91 s (3H) 5.37 s (2H), 5.92 s (1H), 7.15 d (2H), 7.22 m (1H), 7.28 m (2H). Selected IR bands (ν in cm^{-1}): 1645 m, 1598 m, 1529 m, 1451 m, 1364 m, 1343 m, 1231 m, 1156 m, 1053 m, 938 m, 788 m, 749 m, 731 s, 692 m, 640 m, 510 m, 460 m.



9 **20** **21**

3-CF_3-4-methoxy-6-methylpyridone and 5-CF_3-4-methoxy-6-methylpyridone (20 and 21)

Methylated pyridone **9** (150 mg, 1.1 mmol) was dissolved in ~40 mL of DCM. An 18 mL aqueous solution containing $NaSO_2CF_3$ (505 mg, 3.3 mmol) was introduced to the round bottom flask with moderate stirring. A 70% aqueous solution of tertbutylhydroperoxide (tBuOOH, 0.75 mL, 5.5 mmol) was added dropwise to the stirred mixture. The reaction was stirred at room temperature overnight. The acidic reaction mixture was neutralized using conc. $NaHCO_3$, and the product was extracted with 3×30 mL DCM. The organic extract was dried with Na_2SO_4 and dried under reduced pressure to yield 160 mg of white, crystalline solid with a slight green tint (71.5% yield). Separation of the two products by column chromatography is ongoing, but mixtures of DCM with small quantities of MeOH appear promising. ^{1}H NMR in $CDCl_3$ (δ in ppm from TMS) **20:** 2.35 s (3H), 3.89 s (3H), 5.89 s (1H), 12.8 s (1H); **21:** 2.48 q (3H), 3.82 s (3H), 5.82 s (1H), 12.8 s (1H). *The defining characteristic of the ^{1}H NMR specta of the two mono-trifluoromethyl, 4-OMe pyridone regioisomers **20** and **21** is the presence (or absence) of ^{1}H-^{19}F spin coupling of the 6-methyl protons with the adjacent 5-CF_3 group (as in **21**).* ^{19}F NMR in $CDCl_3$: -59.12. -56.89, -54.43, -54.16. Selected IR bands (ν in cm^{-1}) **20:** 1677 s, 1368 w, 1312 w, 1258 m, 1235 s, 1214 m, 1182 s, 1123 vs, 1196 m, 1139 w; **21:** 1647 vs, 1477 w, 1355 w, 1104 m, 1035 m. (Accuracy Questionable) HRMS (ESI) m/z calculated for $[C_8H_8F_3NO_2]^+$ (M+Na)+: 230.03990, 231.04310; found: 230.04040, 231.04350.



2 **22**

3,5-bis(CF_3)-4-hydroxy-6-methylpyridone (22)

Pyridone **2** (150 mg, 1.2 mmol) was slurried in ~40 mL of DCM. A 20 mL aqueous solution containing $NaSO_2CF_3$ (505 mg, 3.3 mmol) was introduced to the round bottom flask with moderate stirring. A 70% aqueous solution of tertbutylhydroperoxide (tBuOOH, 0.75 mL, 5.5 mmol) was added dropwise to the stirred mixture. The reaction was stirred at room temperature overnight, at which point all solids had dissolved. The acidic reaction mixture was neutralized using conc. $NaHSO_4$. Conc. $NaHCO_3$ proved to be too basic, leaving the desired product deprotonated in the aqueous layer. The presence of **22** in the aqueous layer was visible as a light green tint to the water. After neutralization, the product was extracted with 3×30 mL DCM. The organic extract was dried with Na_2SO_4 and dried under reduced pressure to yield 135 mg of white, crystalline solid with a slight green tint (43% yield). Silica TLC with DCM:MeOH 10:1 resulted in a streak with at least two distinguishable bands. Purification by column chromatography is ongoing. ^{1}H NMR in $CDCl_3$ (δ in ppm from TMS) **crude 22:** 2.61 q (3H), 11.94 s (1H), 13.89 s (1H), 14.40 s (1H). ^{19}F NMR in $CDCl_3$ **crude 22:** -80.36, -63.88, -63.54, -56.51, -55.434 (major component), -55.428 (major component).

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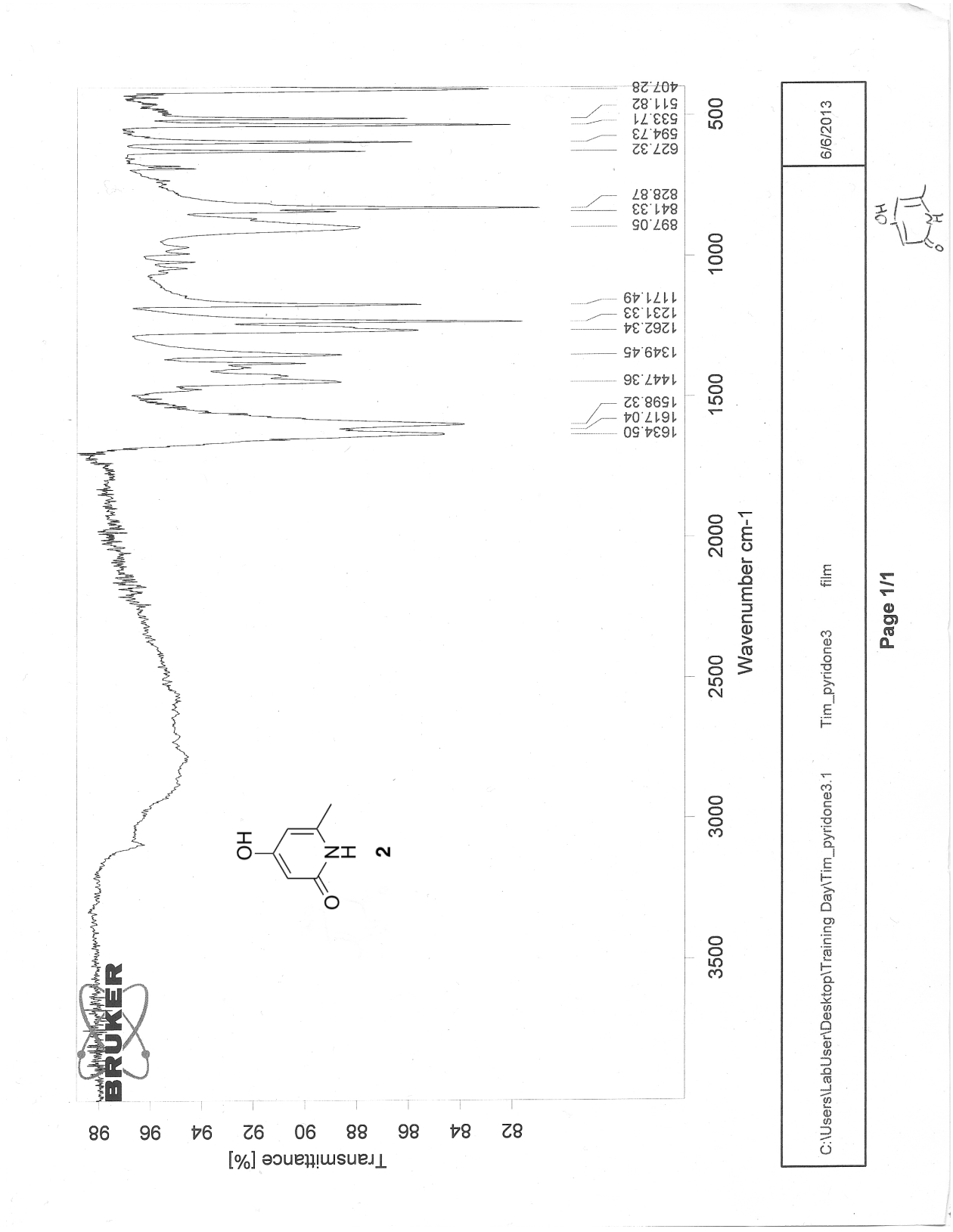
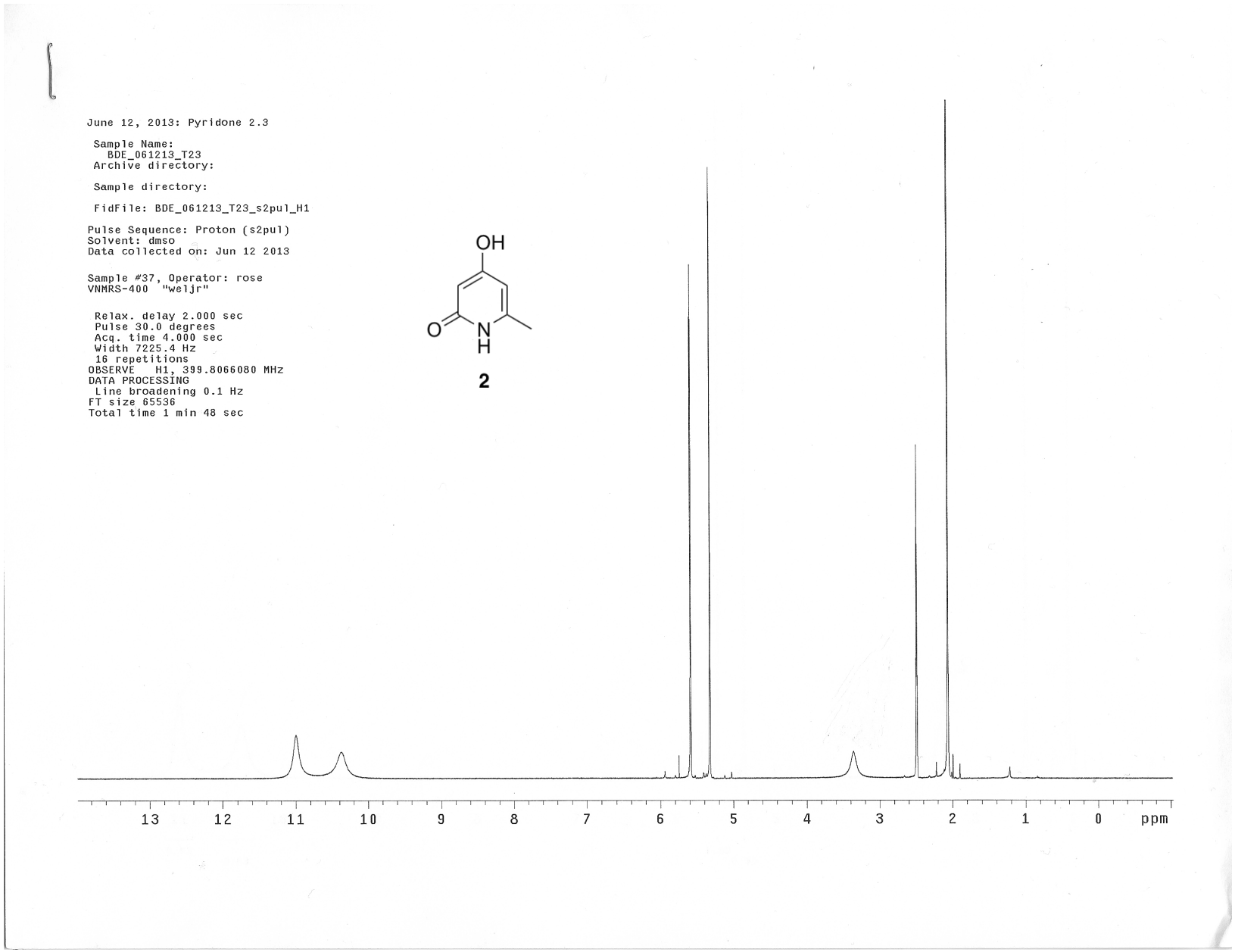
Supplementary Information

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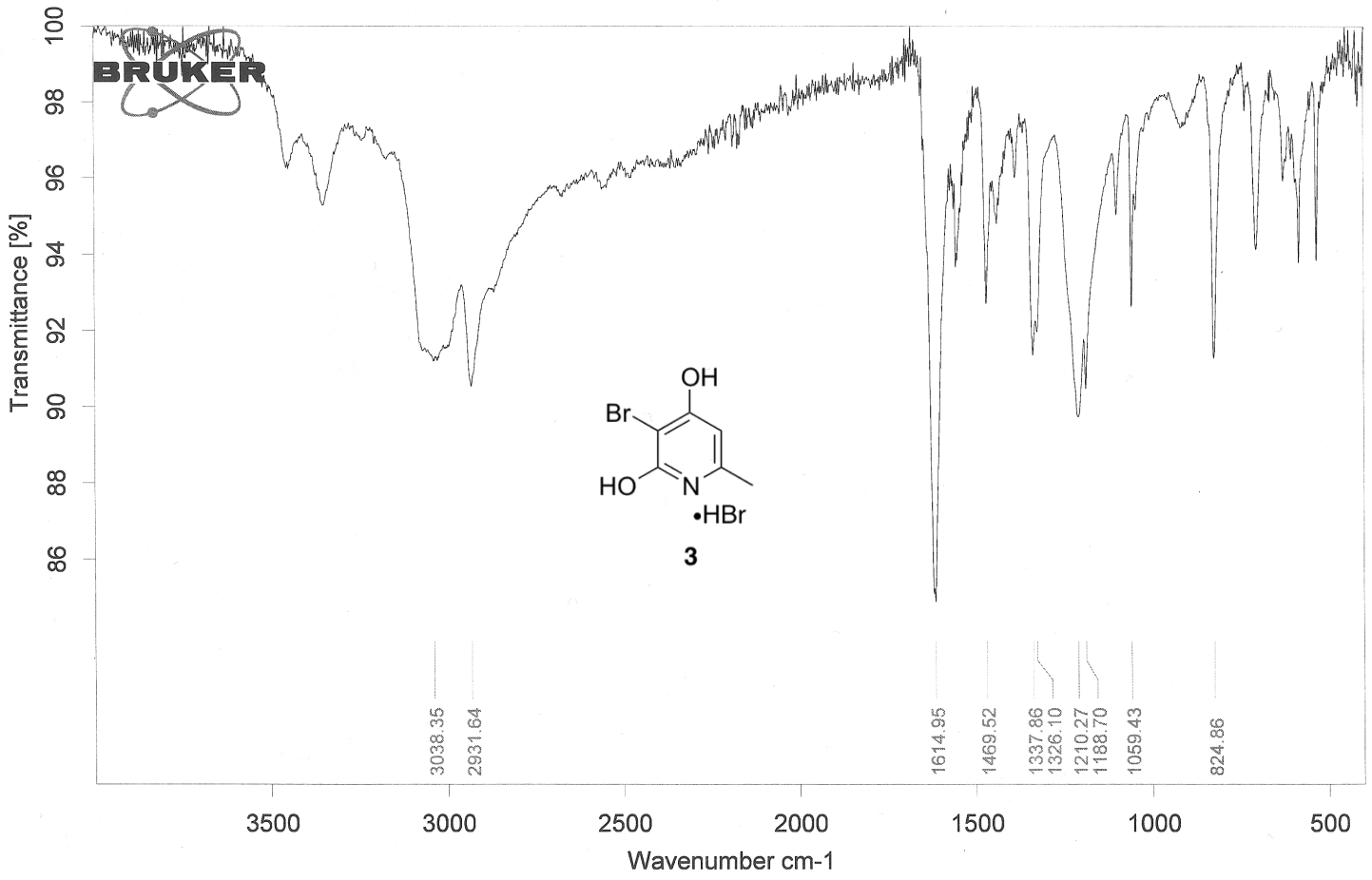
0
ppm



C:\Users\LabUser\Desktop\Training Day\bromopyridine 3.2	bromopyridine 3.2	film	6/11/2013

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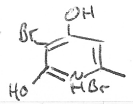
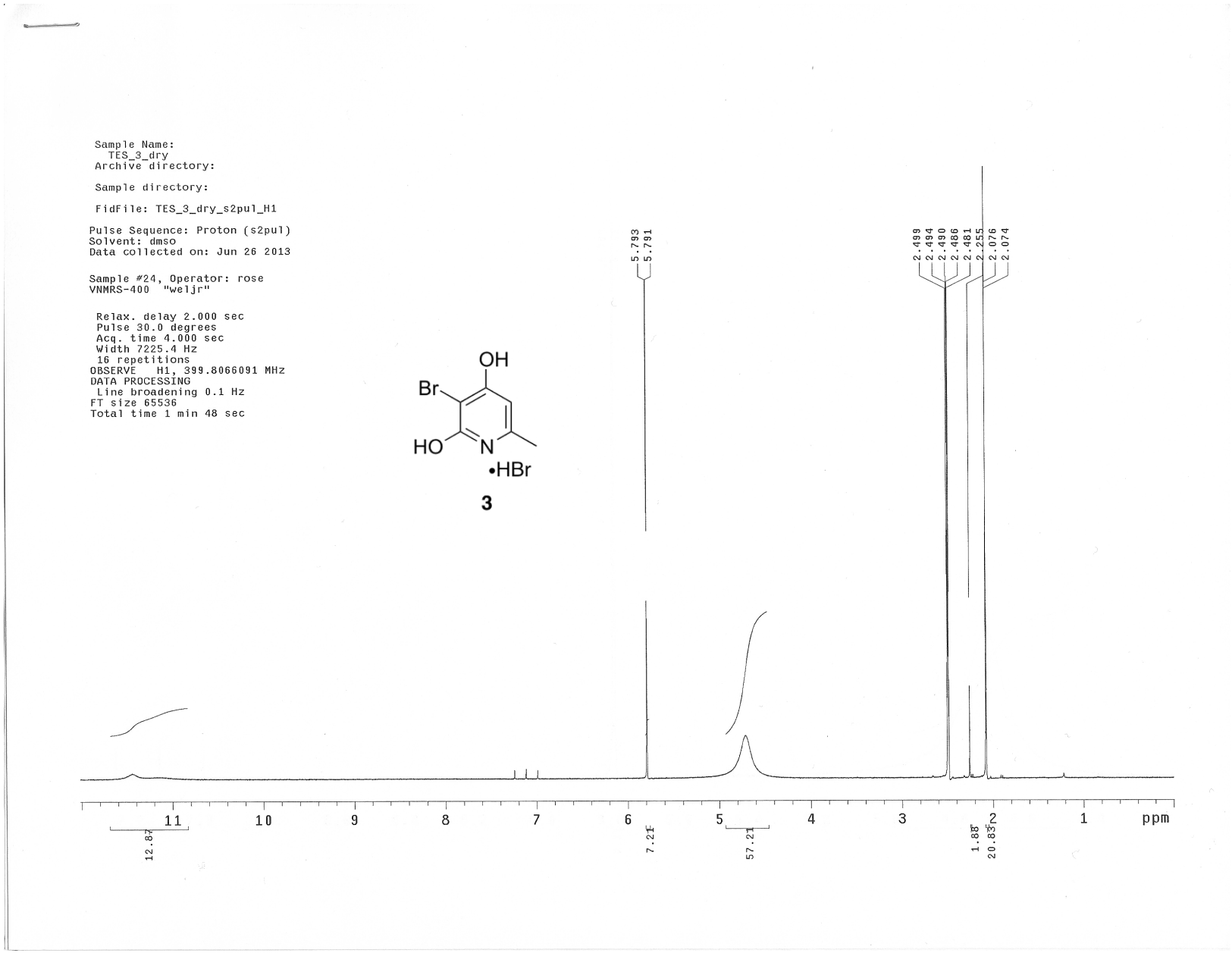
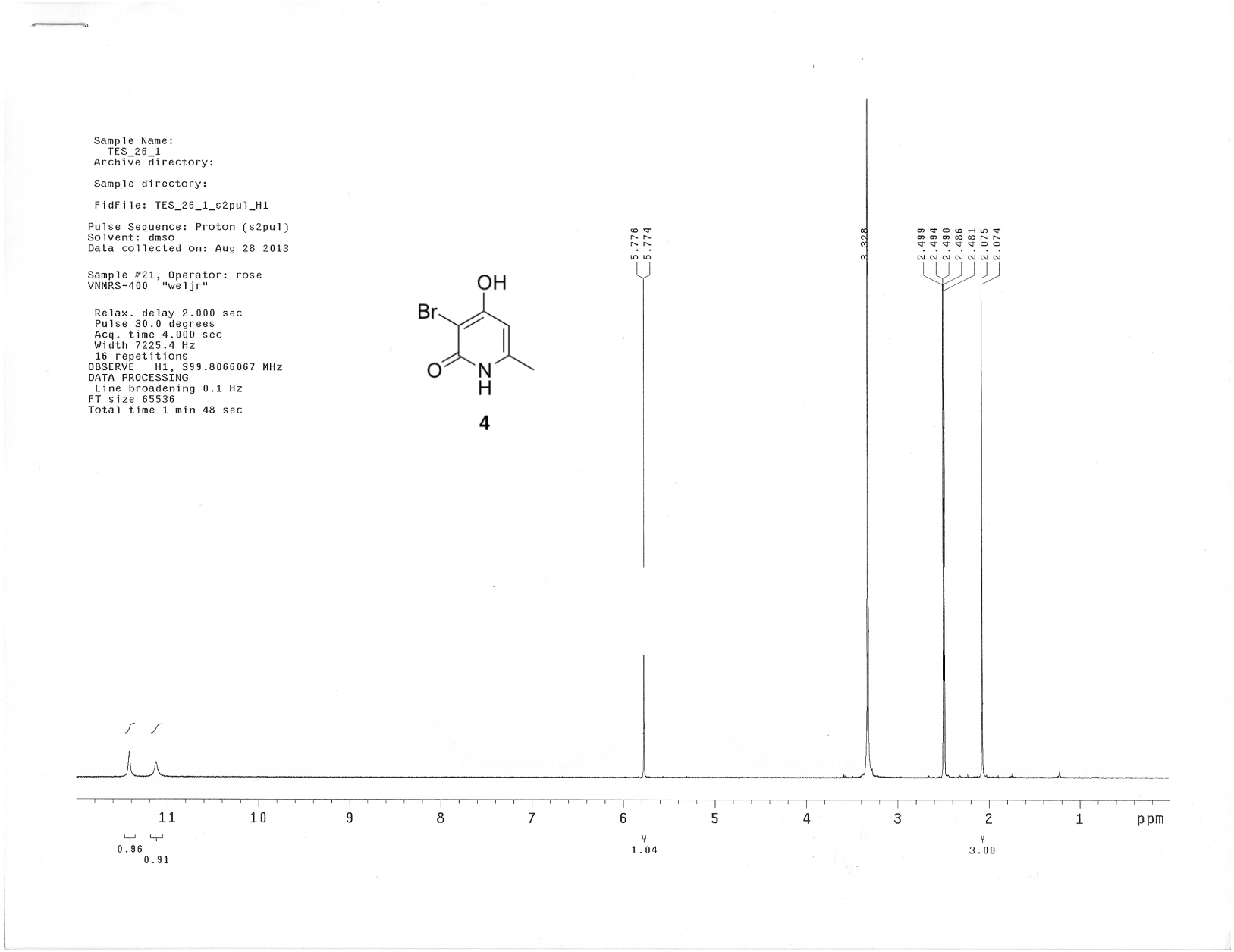
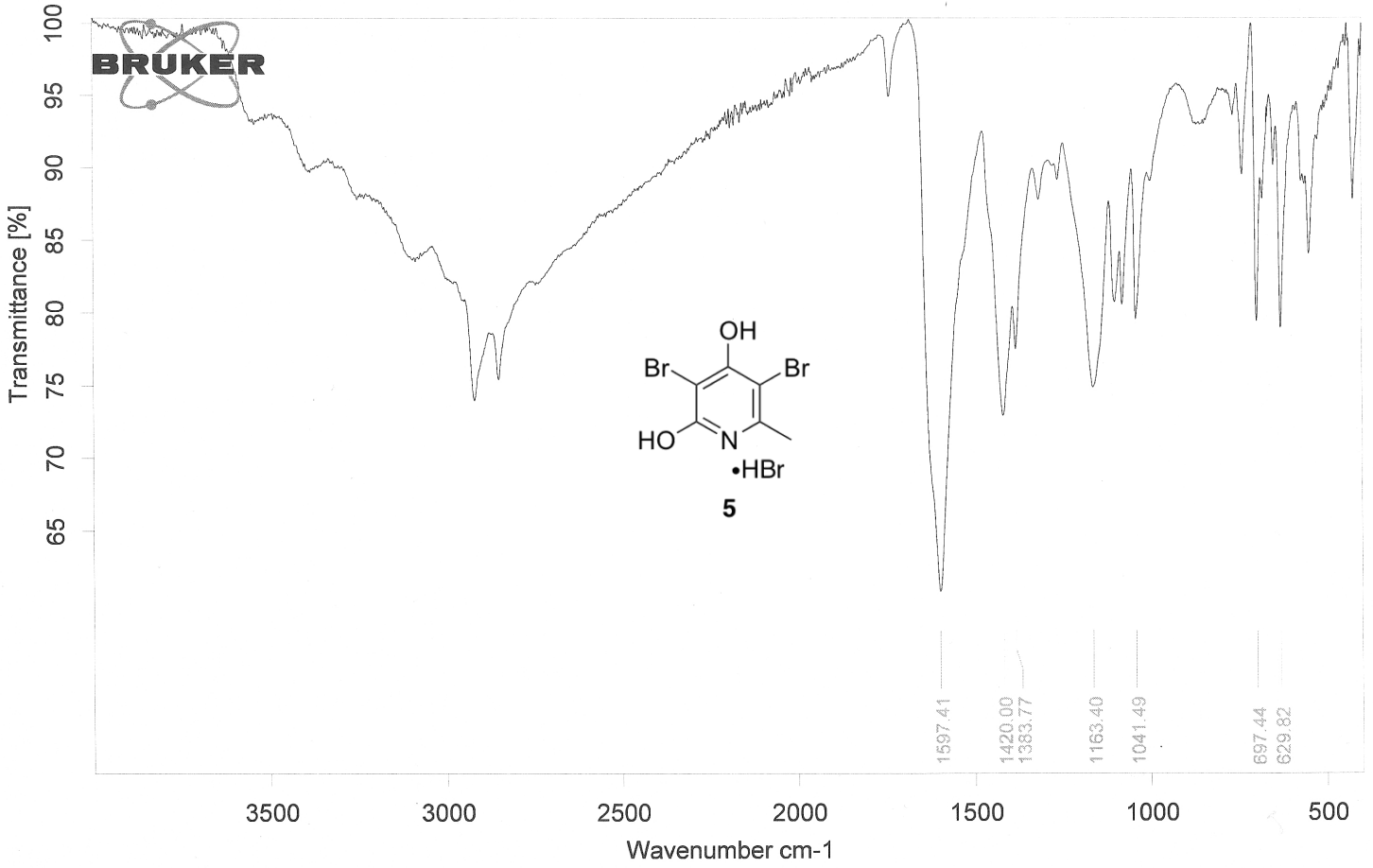



Sample Name:
TES_3_dry
Archive directory:
Sample directory:
FidFile: TES_3_dry_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: dmso
Data collected on: Jun 26 2013
Sample #24, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 7225.4 Hz
16 repetitions
OBSERVE H1, 399.8066091 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
OH
Br
HO
N
•HBr
3
5.793
5.791
2.499
2.494
2.490
2.486
2.481
2.255
2.076
2.074
11
10
9
8
7
6
5
4
3
2
1
ppm
12.83
7.21
57.21
1.88
20.83

BRUKER
Transmittance [%]
98
96
94
92
90
88
86
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
798.90
1044.09
1345.63
1381.90
1459.58
1563.52
1595.82
1625.13
OH
Br
O
N
H
4
C:\Users\LabUser\Desktop\Training Day\neutral_mbp_12_1.0
neutral_mbp_12_1
film
7/10/2013
Page 1/1


Sample Name:
TES_26_1
Archive directory:
Sample directory:
FidFile: TES_26_1_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: dmso
Data collected on: Aug 28 2013
Sample #21, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 7225.4 Hz
16 repetitions
OBSERVE H1, 399.8066067 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
OH
Br
O
N
H
4
5.776
5.774
3.328
2.499
2.494
2.490
2.486
2.481
2.075
2.074
11
10
9
8
7
6
5
4
3
2
1
ppm
0.96
0.91
1.04
3.00



C:\Users\LabUser\Desktop\Training Day\35Br4OHPyridone.1	35Br4OHPyridone	film	4/15/2014

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Sample Name:
TES_31_1
Archive directory:

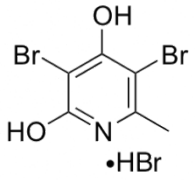
Sample directory:

FidFile: TES_31_1_s2pul_H1

Pulse Sequence: Proton (s2pul)
Solvent: dmso
Data collected on: Sep 3 2013

Sample #11, Operator: rose
VNMRS-400 "weljr"

Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 7225.4 Hz
16 repetitions
OBSERVE H1, 399.8066075 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec



5

Transmittance [%]
95
90
85
80
75
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
1669.97
1624.44
1551.94
1440.34
1406.91
1395.87
1377.66
1232.90
1028.67
950.84
815.74
748.55
633.91
624.98
611.91
568.41
527.56
430.67
421.20
OH
Br
O
O
7
BRUKER
C:\Users\LabUser\Desktop\Training Day\3Br4OHpyrone.0
18
3Br4OHpyrone
film
4/15/2014
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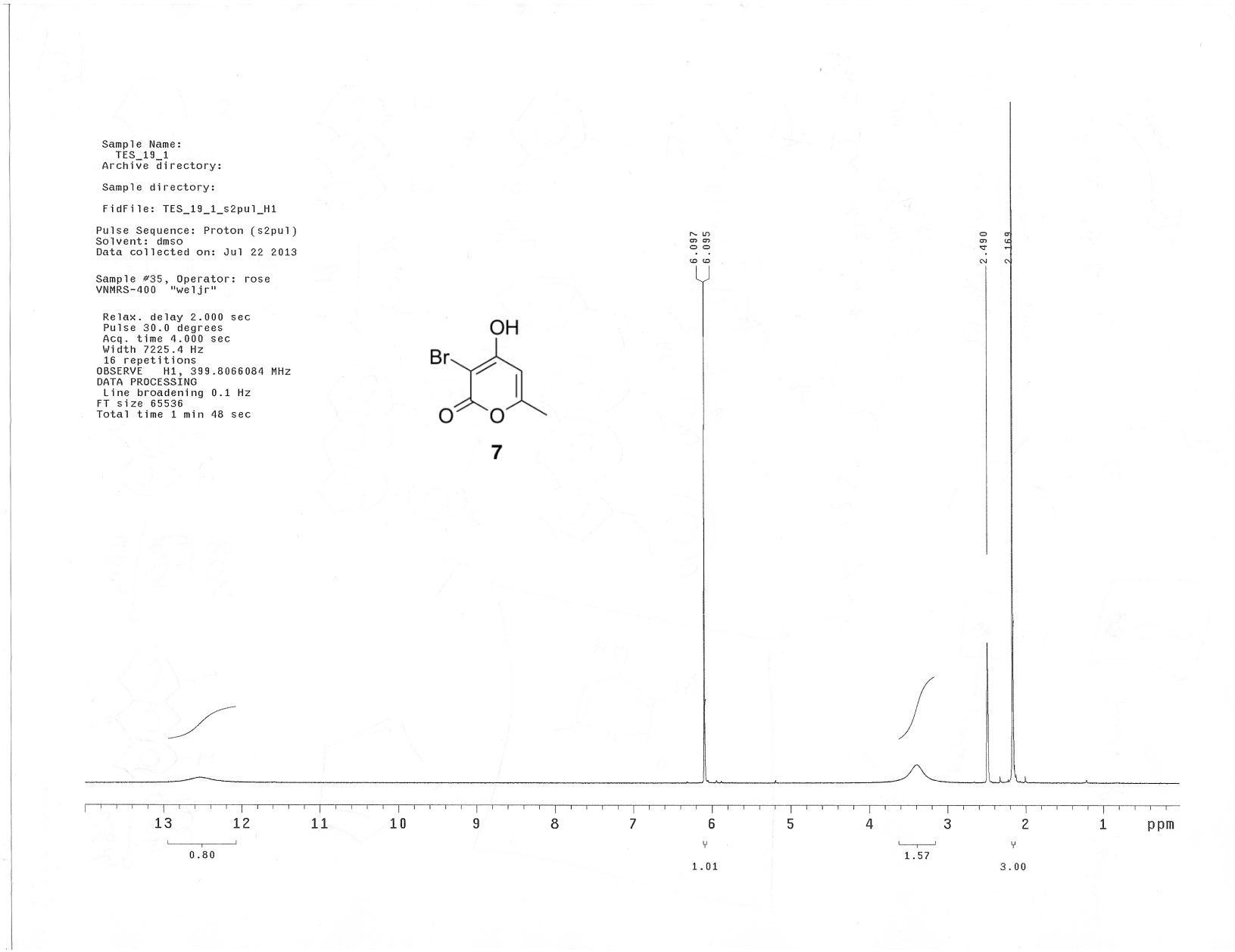
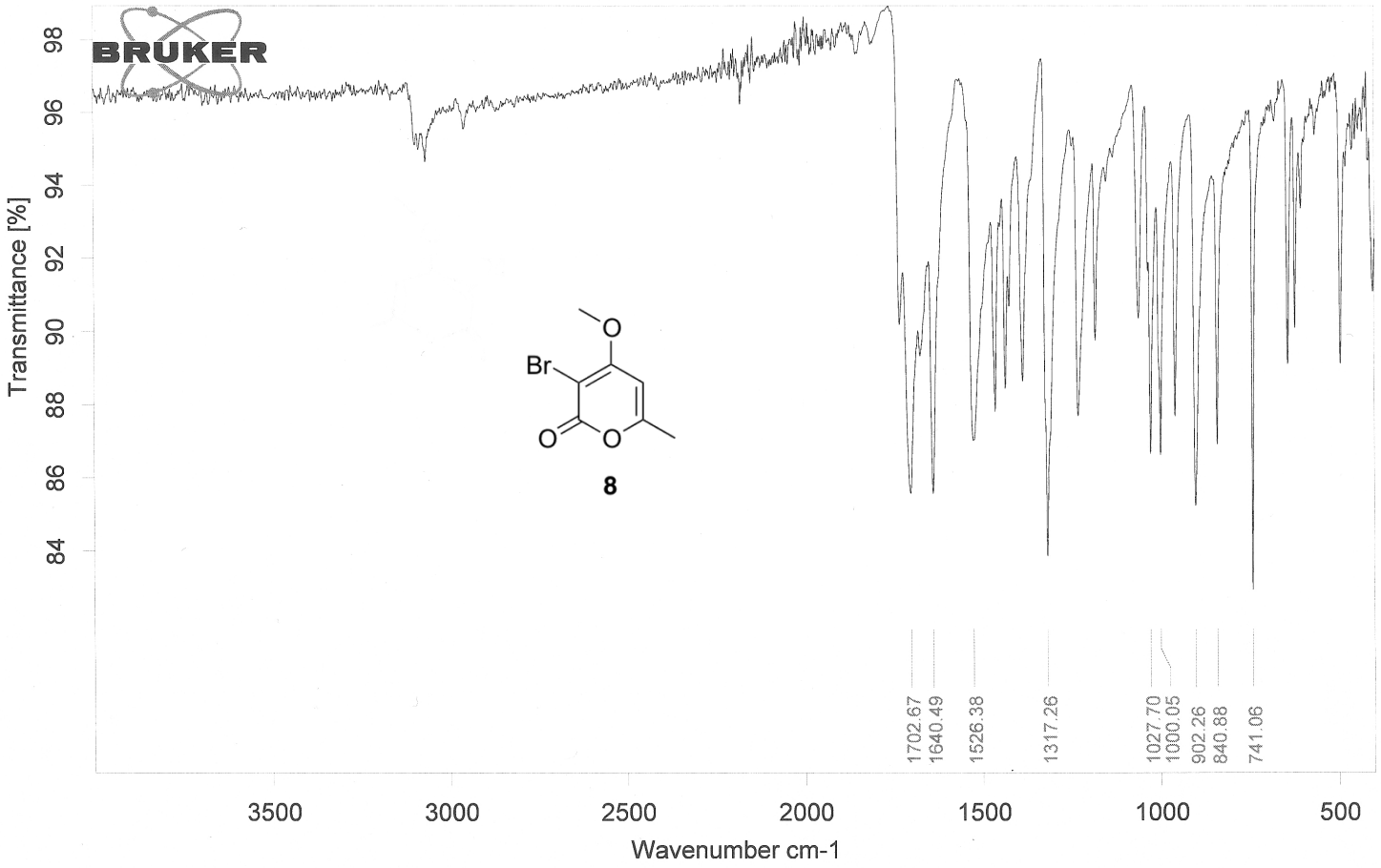

Sample Name:
TES_19_1
Archive directory:
Sample directory:
FidFile: TES_19_1_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: dmso
Data collected on: Jul 22 2013
Sample #35, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 7225.4 Hz
16 repetitions
OBSERVE H1, 399.8066084 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
OH
Br
O
O
7
6.097
6.095
2.490
2.169
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.80
1.01
1.57
3.00



C:\Users\LabUser\Desktop\Training Day\3Br4MeOpyrone.0	3Br4MeOpyrone	film	4/15/2014

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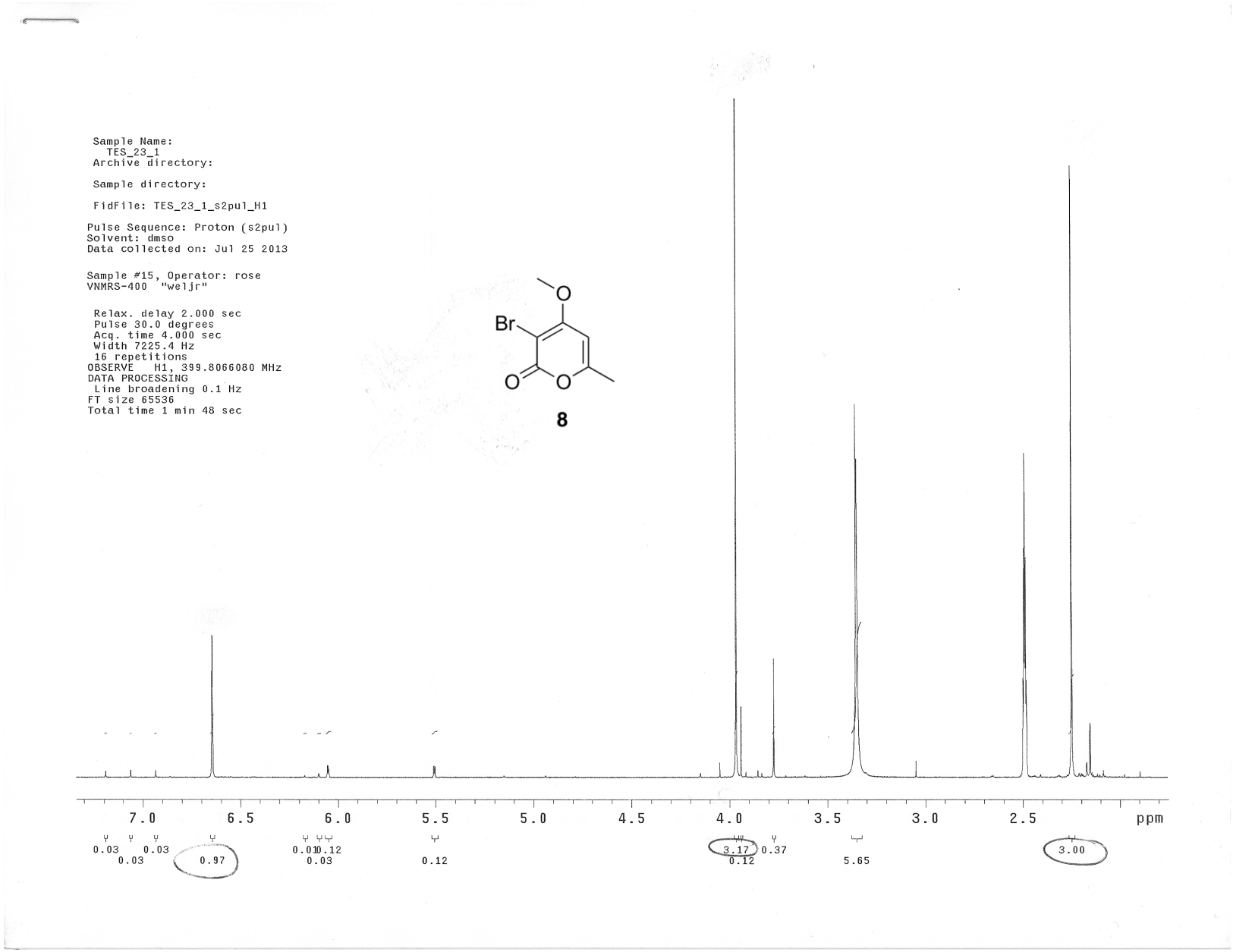
Sample Name:
TES_23_1
Archive directory:
Sample directory:
FidFile: TES_23_1_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: dmso
Data collected on: Jul 25 2013
Sample #15, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 7225.4 Hz
16 repetitions
OBSERVE H1, 399.8066080 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
Br
O
O
O
8
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
0.03
0.03
0.03
0.97
0.01
0.12
0.03
0.12
3.17
0.37
0.12
5.65
3.00

BRUKER
Transmittance [%]
90
80
70
60
50
40
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
1640.12
1445.56
1225.91
1154.58
1055.10
893.72
808.83
791.74
582.21
546.76
428.67
6
C:\Users\LabUser\Desktop\Training Day\4MeONHpyridone.0
4MeONHpyridone
film
4/15/2014
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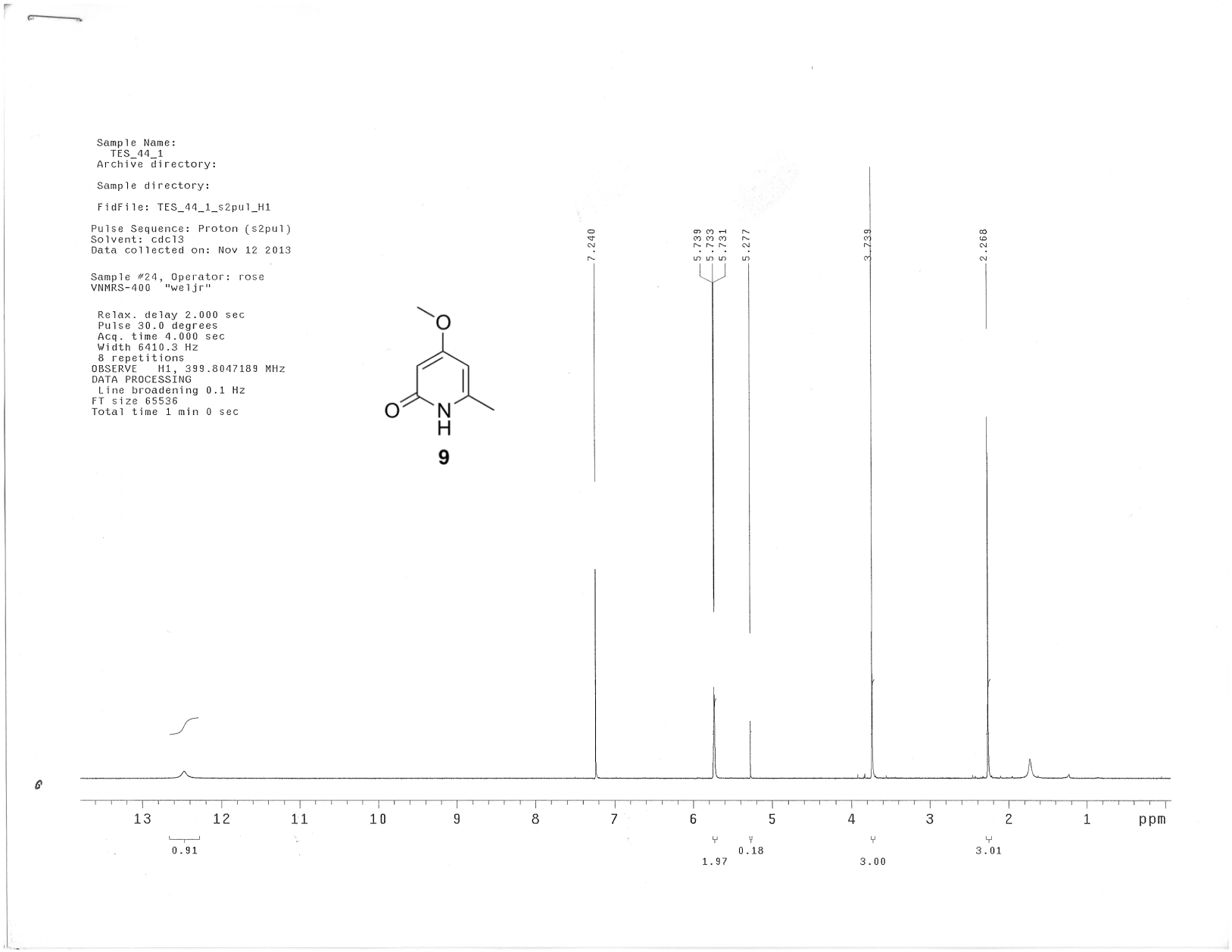
Sample Name:
TES_44_1
Archive directory:
Sample directory:
FidFile: TES_44_1_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Nov 12 2013
Sample #24, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.8047189 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 0 sec
O
O
N
H
9
7.240
5.739
5.733
5.731
5.277
3.739
2.268
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.91
1.97
0.18
3.00
3.01

Transmittance [%]
95
90
85
80
75
70
65
60
55
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
809.11
856.55
923.47
1135.96
1216.46
1243.44
1358.31
1413.09
1560.77
1586.90
1650.75
10
C:\Users\LabUser\Desktop\Training Day\NMe_4MeO_pdn_2.0
NMe_4MeO_pdn_2
film
10/23/2013
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Sample Name:
TES_27_f3
Archive directory:

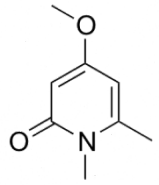
Sample directory:

FidFile: TES_27_f3_s2pul_H1

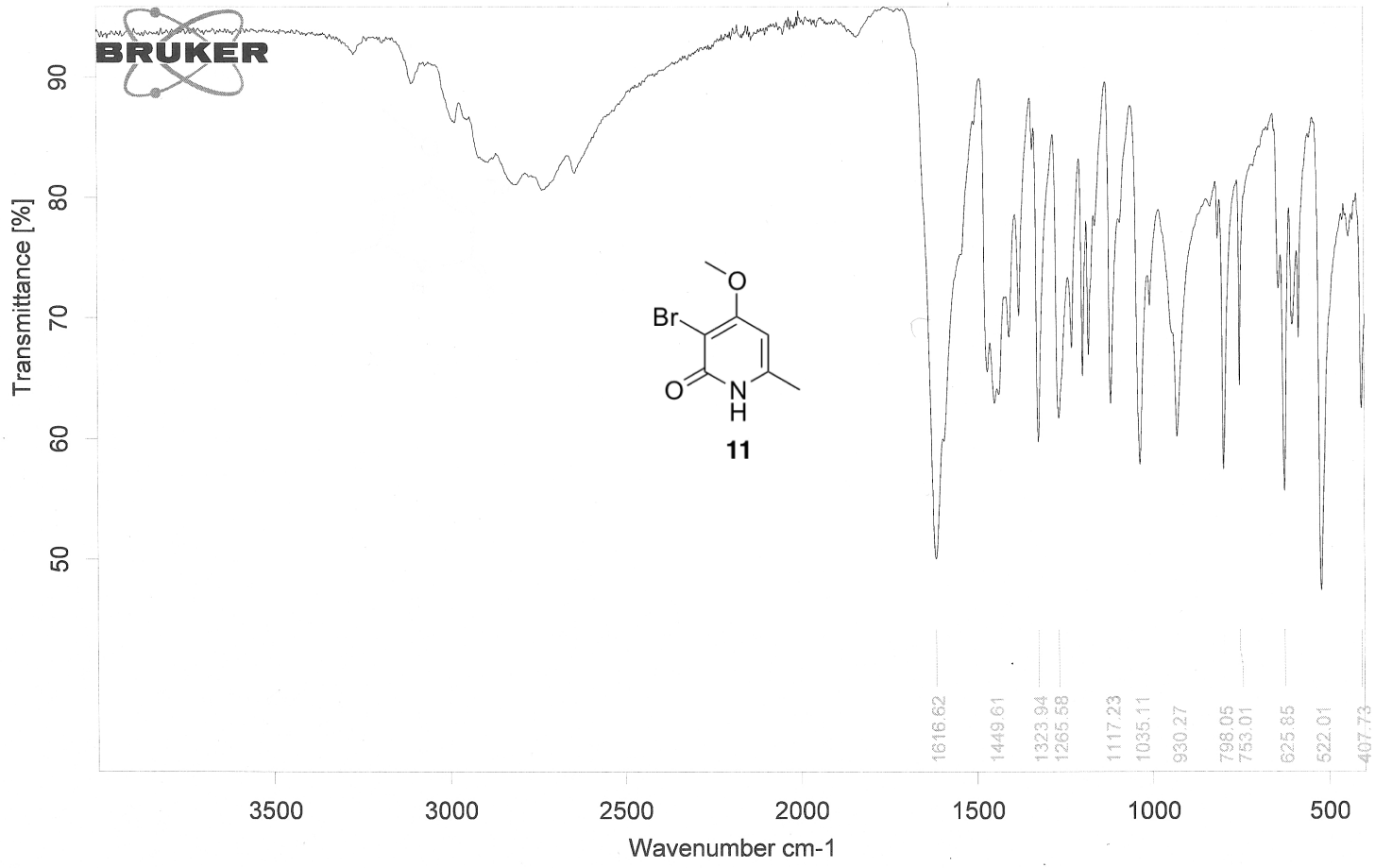
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Aug 27 2013

Sample #24, Operator: rose
VNMRS-400 "weljr"

Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.8047189 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec



10



C:\Users\LabUser\Desktop\Training Day\3Br4MeONHpyridone.0	3Br4MeONHpyridone	film	4/15/2014

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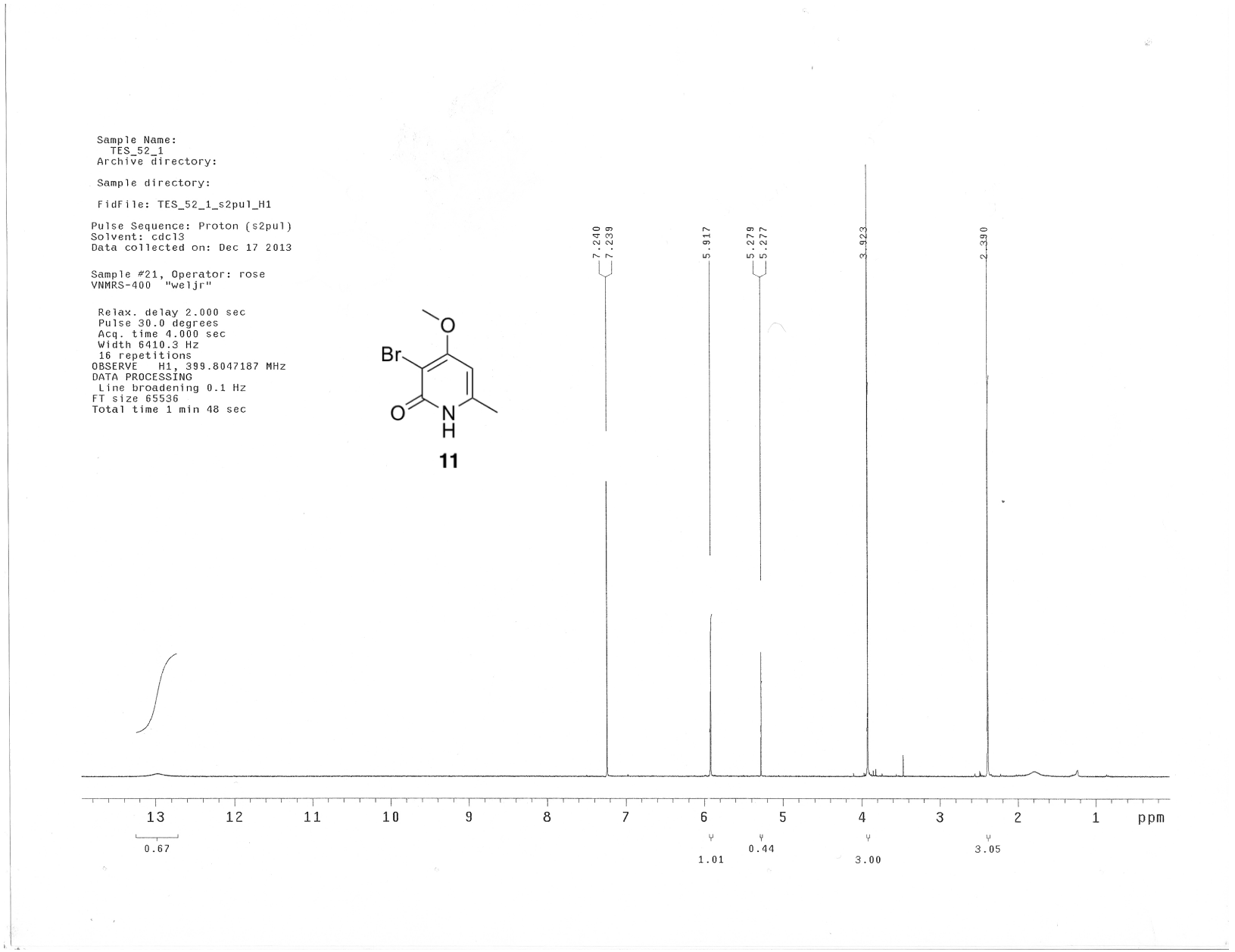
Sample Name:
TES_52_1
Archive directory:
Sample directory:
FidFile: TES_52_1_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Dec 17 2013
Sample #21, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.8047187 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
Br
O
O
N
H
11
7.240
7.239
5.917
5.279
5.277
3.923
2.390
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.67
1.01
0.44
3.00
3.05

BRUKER
Transmittance [%]
100
90
80
70
60
50
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
2919.61
2851.09
1633.37
1591.99
1529.27
1477.46
1447.93
1393.29
1344.02
1237.09
1207.23
1177.24
1144.30
1068.22
1033.46
821.68
814.99
749.30
626.03
470.45
Br
O
N
O
12
C:\Users\LabUser\Desktop\Training Day\3Br4MeONMePyridone.0
3Br4MeONMePyridone
film
4/15/2014
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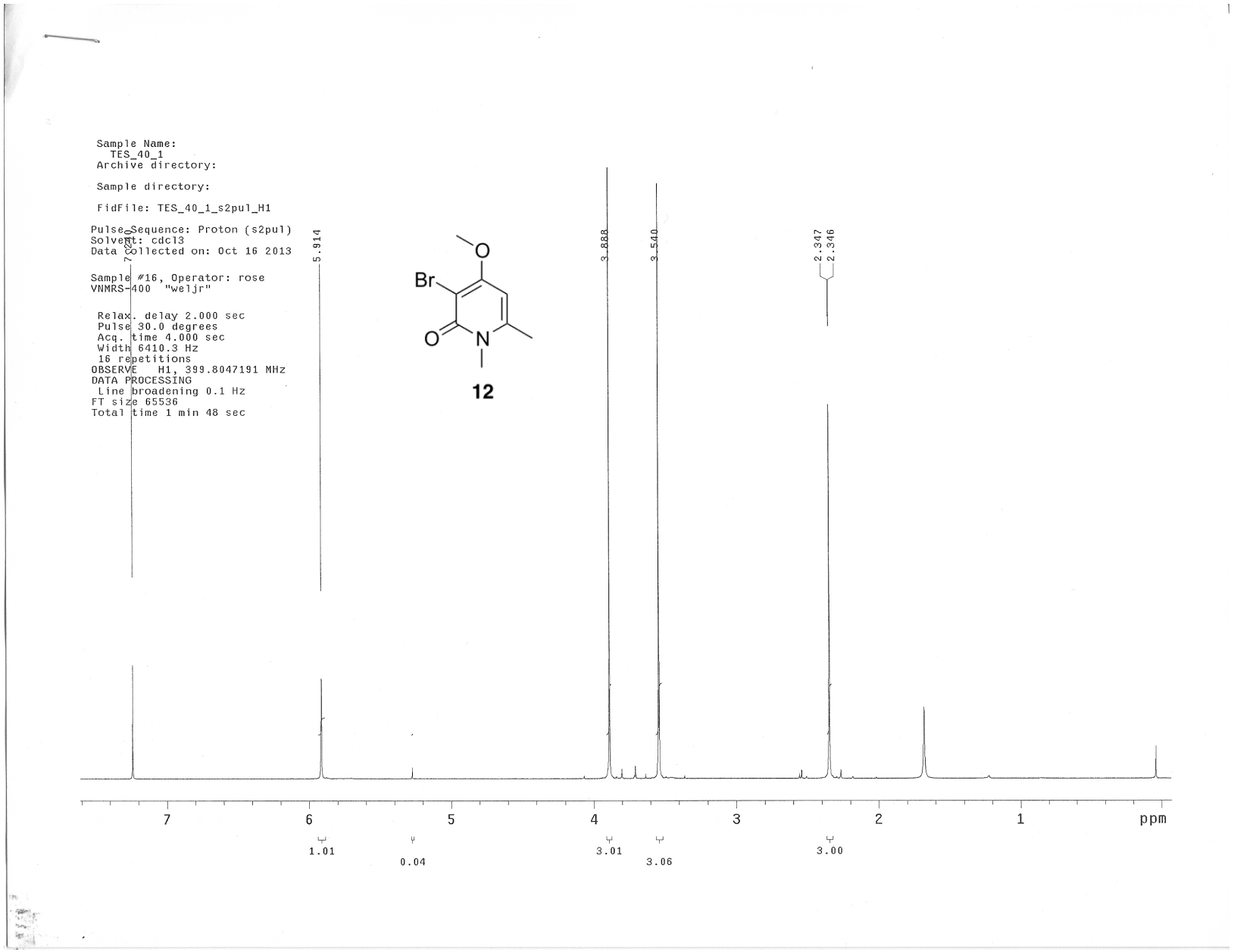
Sample Name:
TES_40_1
Archive directory:
Sample directory:
FidFile: TES_40_1_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Oct 16 2013
Sample #16, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.8047191 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
7.266
5.914
3.888
3.540
2.347
2.346
Br
O
O
N
12
7
6
5
4
3
2
1
ppm
1.01
0.04
3.01
3.06
3.00

BRUKER
Transmittance [%]
80
70
60
50
40
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
1638.77
1597.42
1439.41
1362.46
1230.19
1103.80
1035.22
923.38
798.35
756.34
696.72
645.77
623.58
586.38
529.36
418.99
Br
O
N
H
O
Br
13
C:\Users\LabUser\Desktop\Training Day\35Br4MeONHpyridone.0
35Br4MeONHpyridone
film
4/15/2014
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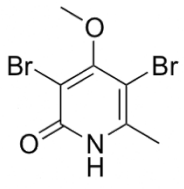
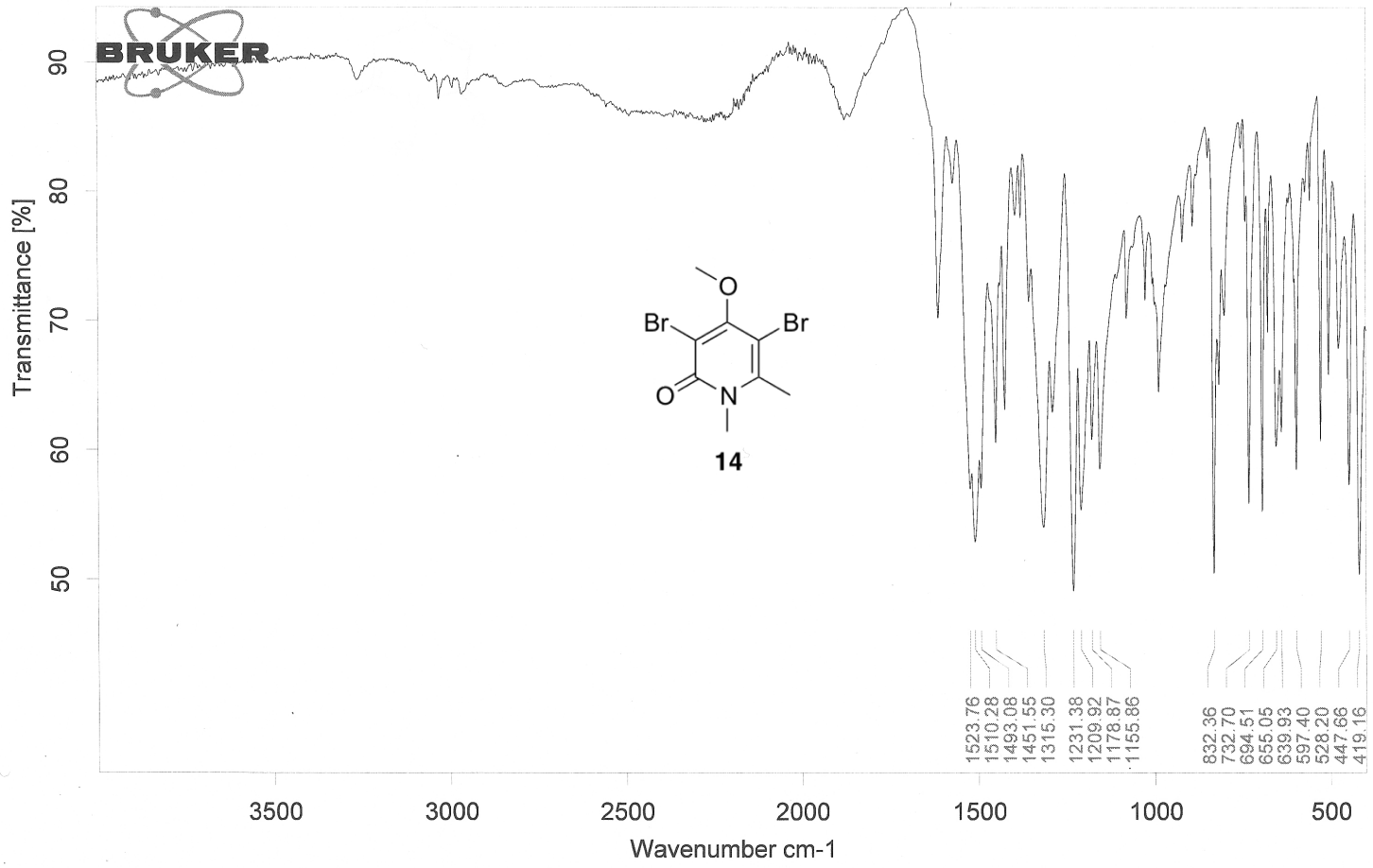
exp1 Proton

SAMPLE		SPECIAL	
date	Sep 25 2013	temp	not used
solvent	cdcl3	gain	not used
file	/home/space/d~	spin	20
	ata/TES_35_4_s2pul~	hst	0.008
	_H1.fid	pw90	15.000
ACQUISITION		alfa	10.000
sw	6410.3	FLAGS	
at	4.000	il	n
np	51282	in	n
fb	4000	dp	y
bs	32	hs	nn
ss	2	PROCESSING	
d1	2.000	lb	0.10
nt	16	fn	65536
ct	16	DISPLAY	
TRANSMITTER		sp	-33.1
tn	H1	wp	3204.9
sfrq	399.807	rfl	3708.7
tof	399.8	rfp	2894.6
tpwr	60	rp	0.1
pw	5.000	lp	0
DECOUPLER		PLOT	
dn	C13	wc	250
dof	0	sc	0
dm	nnn	vs	136
dmm	c	th	46
dpwr	35	ai ph	
dmf	29412		



13



C:\Users\LabUser\Desktop\Training Day\1Bz4OHpyridone.0	1Bz4OHpyridone	film	4/15/2014

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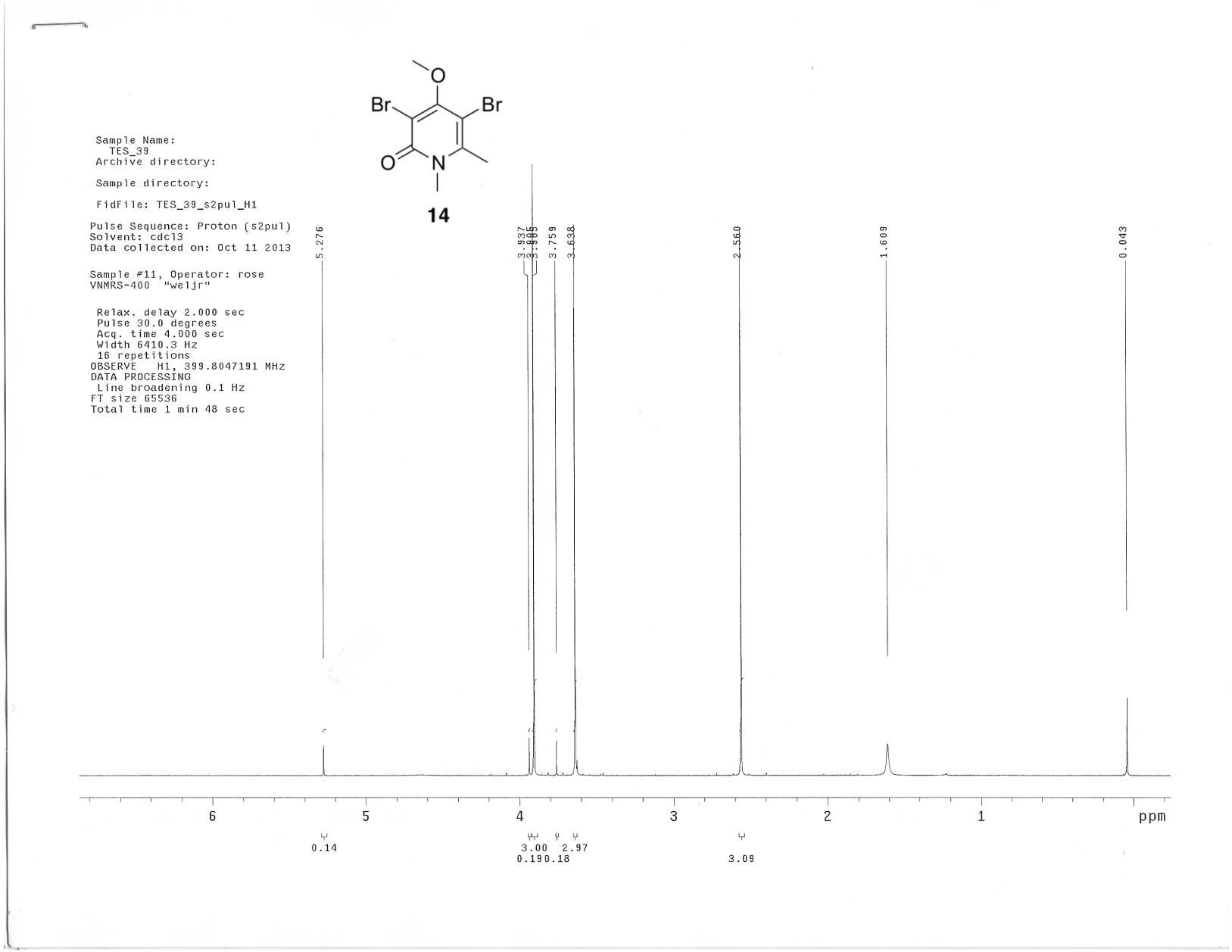
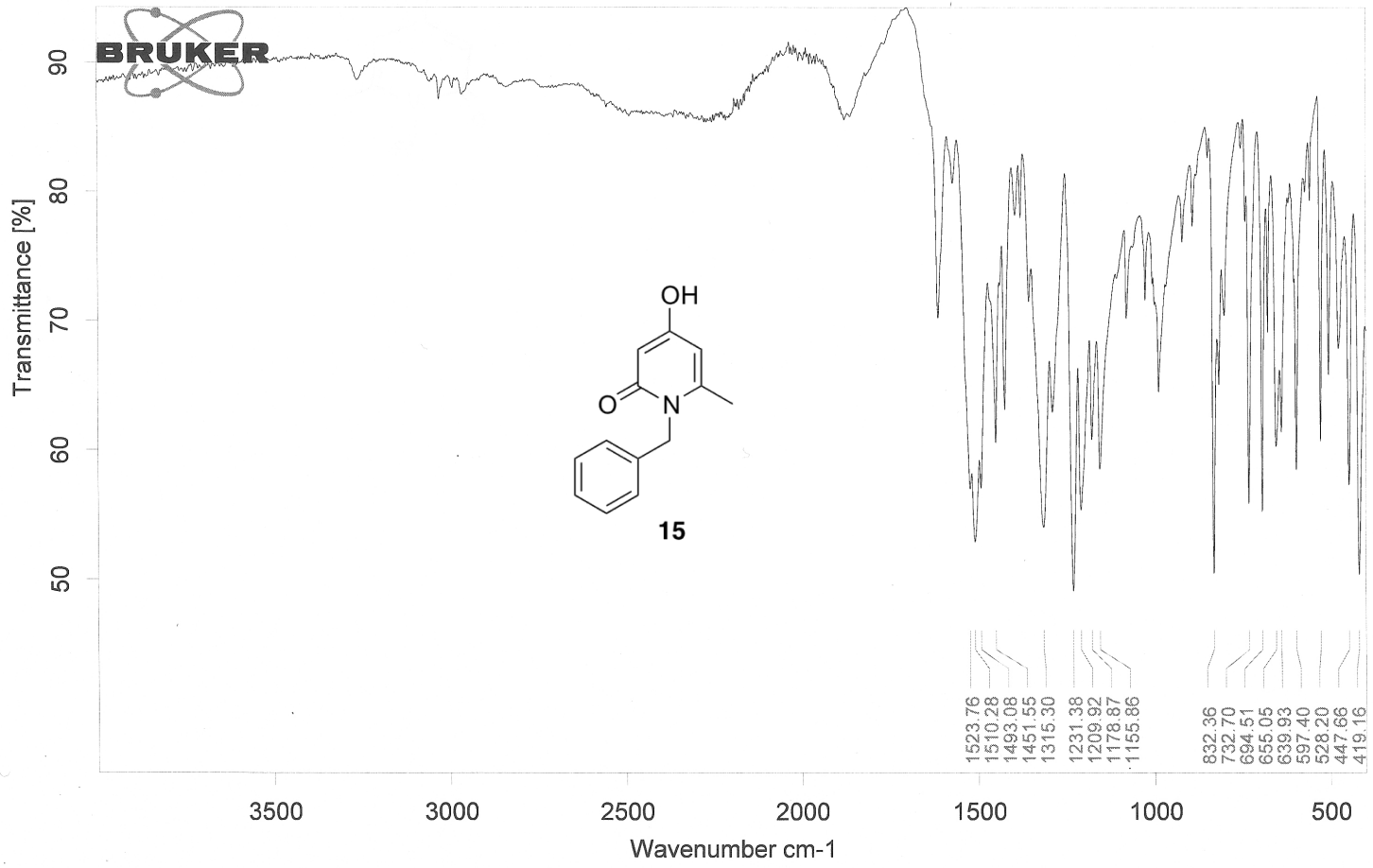
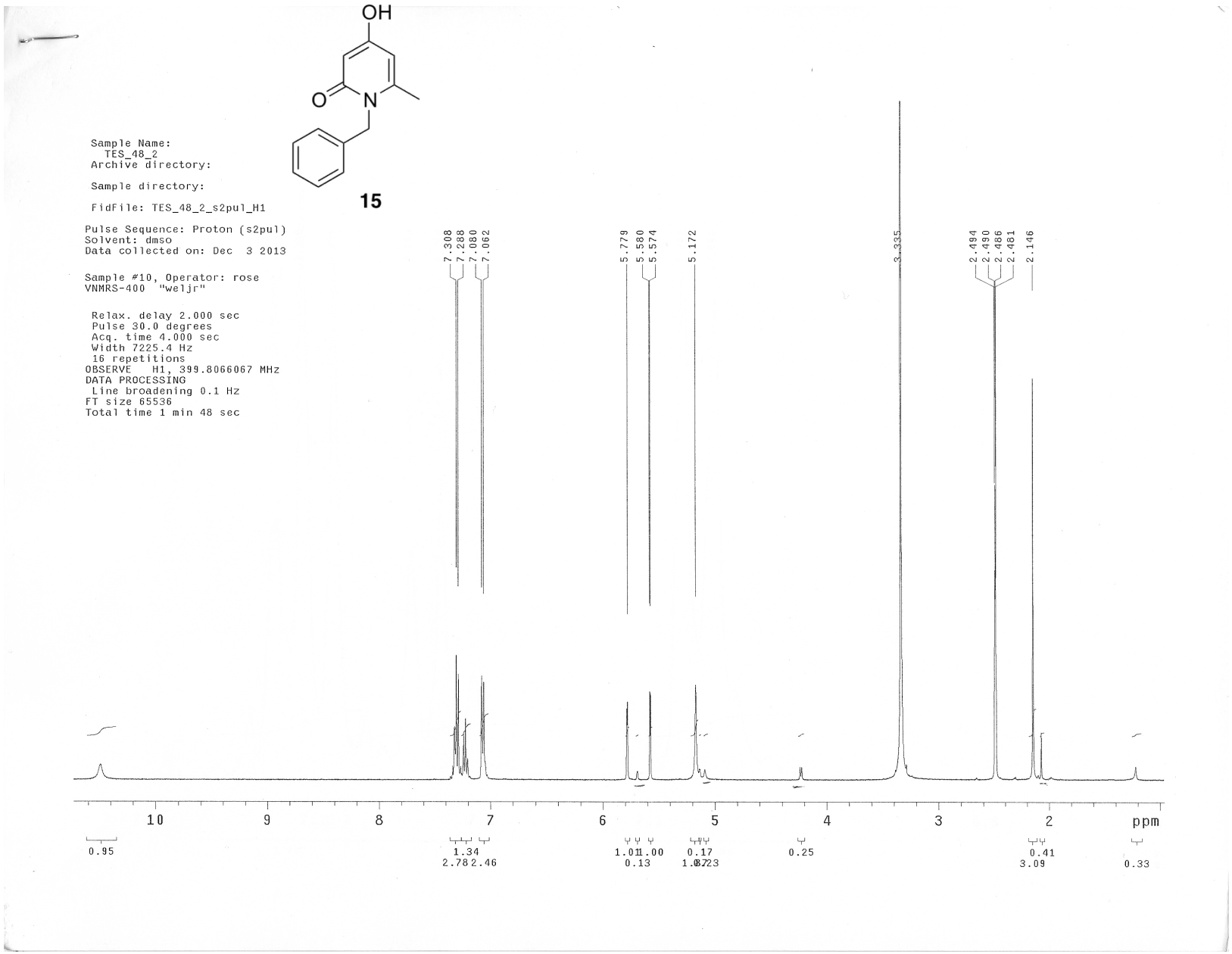
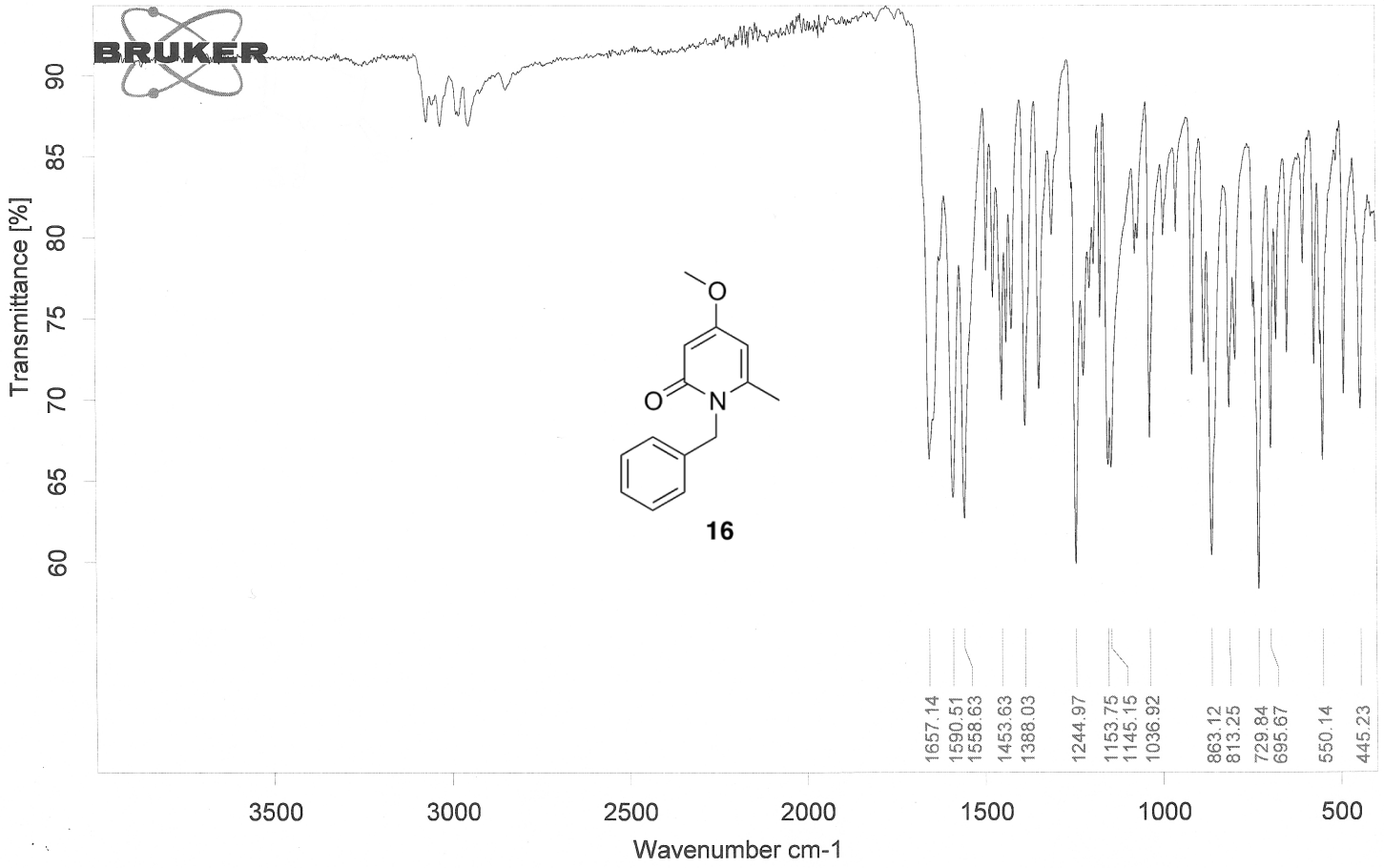

Sample Name:
TES_39
Archive directory:
Sample directory:
FidFile: TES_39_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Oct 11 2013
Sample #11, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.8047191 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
Br
Br
O
O
N
14
5.276
3.937
3.885
3.759
3.638
2.560
1.609
0.043
6
5
4
3
2
1
ppm
0.14
3.00
0.19
0.18
2.97
3.09



C:\Users\LabUser\Desktop\Training Day\1Bz4OHpyridone.0	1Bz4OHpyridone	film	4/15/2014


OH
O
N
15
Sample Name:
TES_48_2
Archive directory:
Sample directory:
FidFile: TES_48_2_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: dmso
Data collected on: Dec 3 2013
Sample #10, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 7225.4 Hz
16 repetitions
OBSERVE H1, 399.8066067 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
7.308
7.288
7.080
7.062
5.779
5.580
5.574
5.172
3.335
2.494
2.490
2.486
2.481
2.146
10
9
8
7
6
5
4
3
2
ppm
0.95
1.34
2.78
2.46
1.01
1.00
0.13
0.17
0.25
0.41
3.09
0.33



C:\Users\LabUser\Desktop\Training Day\1Bz4MeOpyridone.0	1Bz4MeOpyridone	film	4/15/2014

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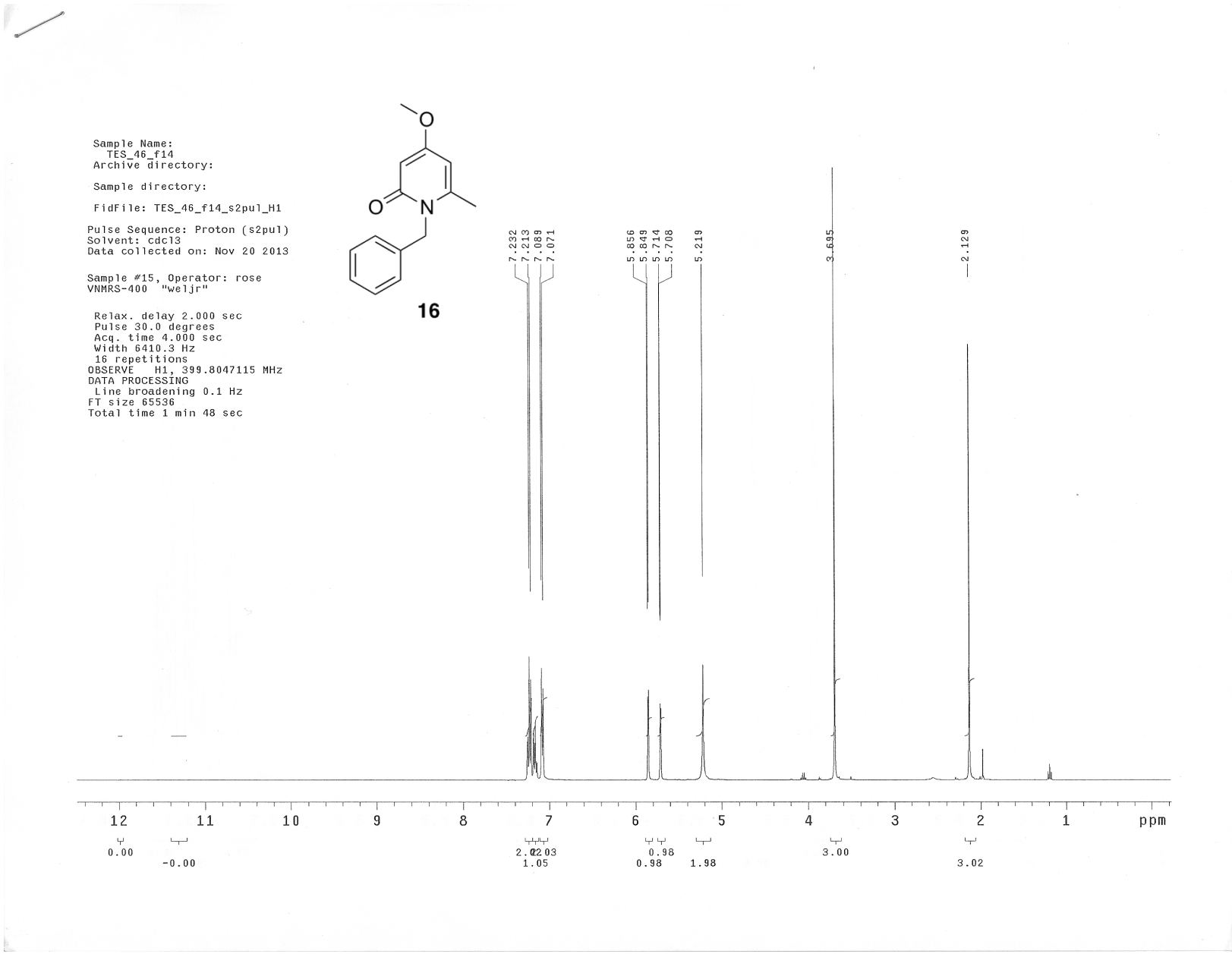
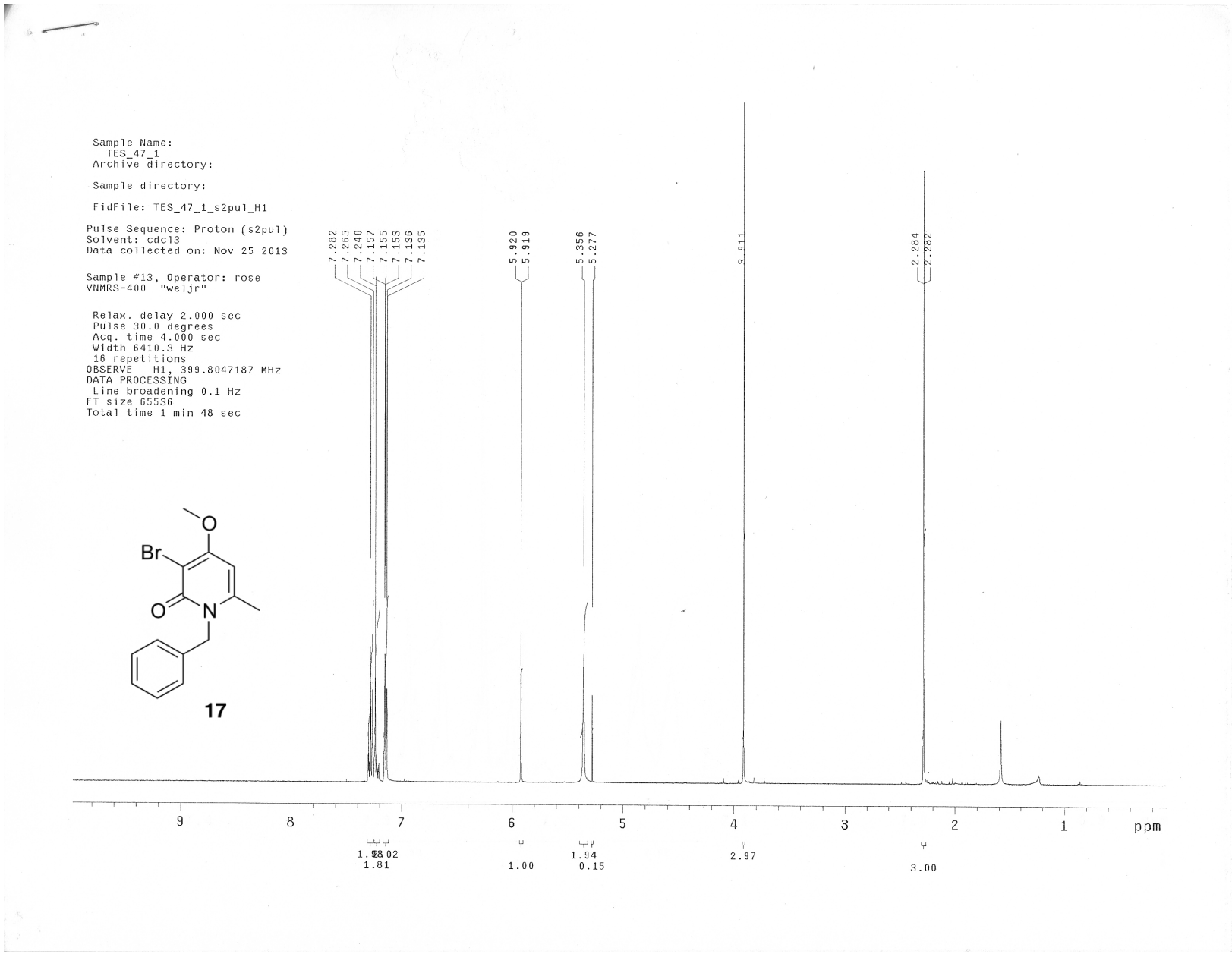
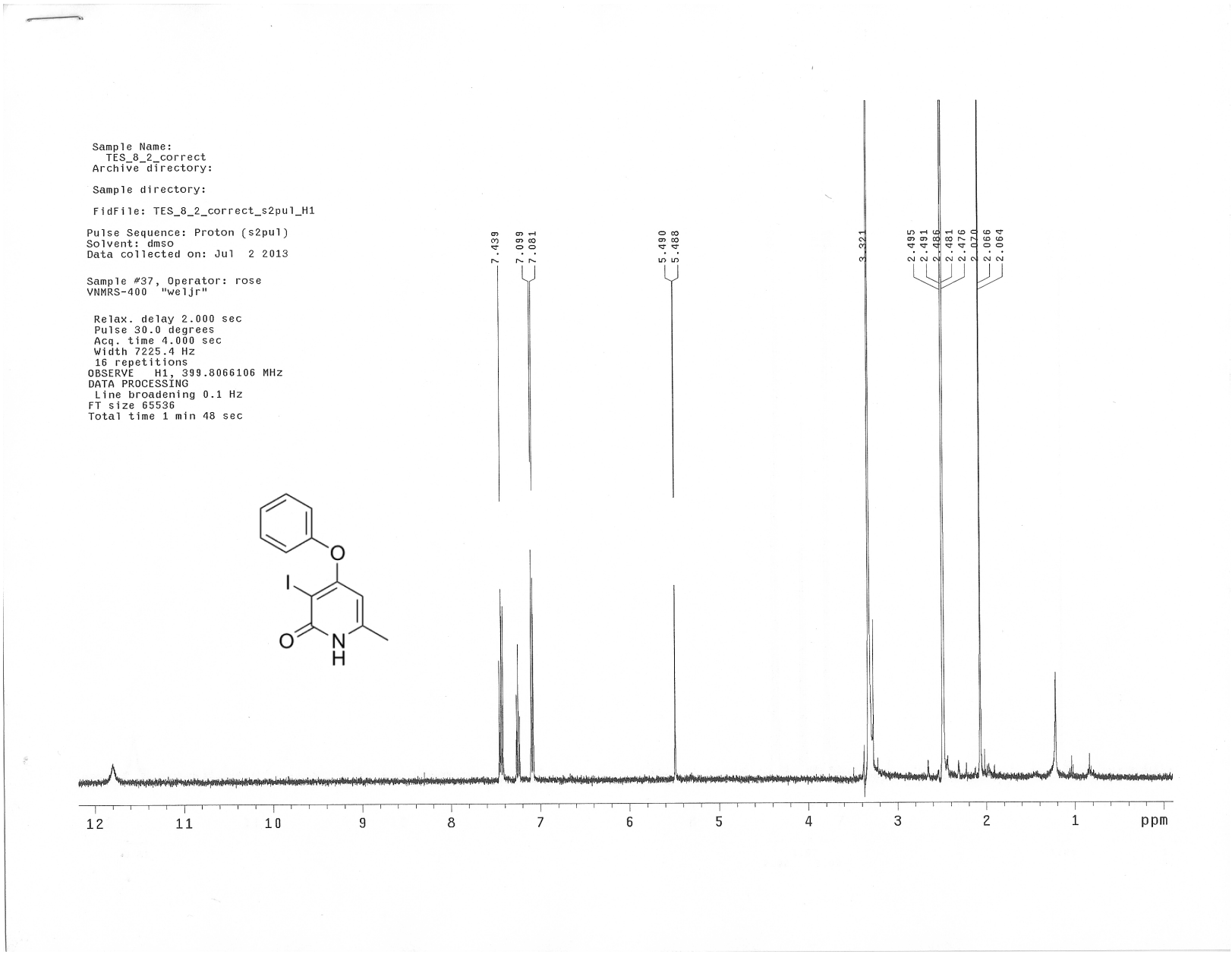
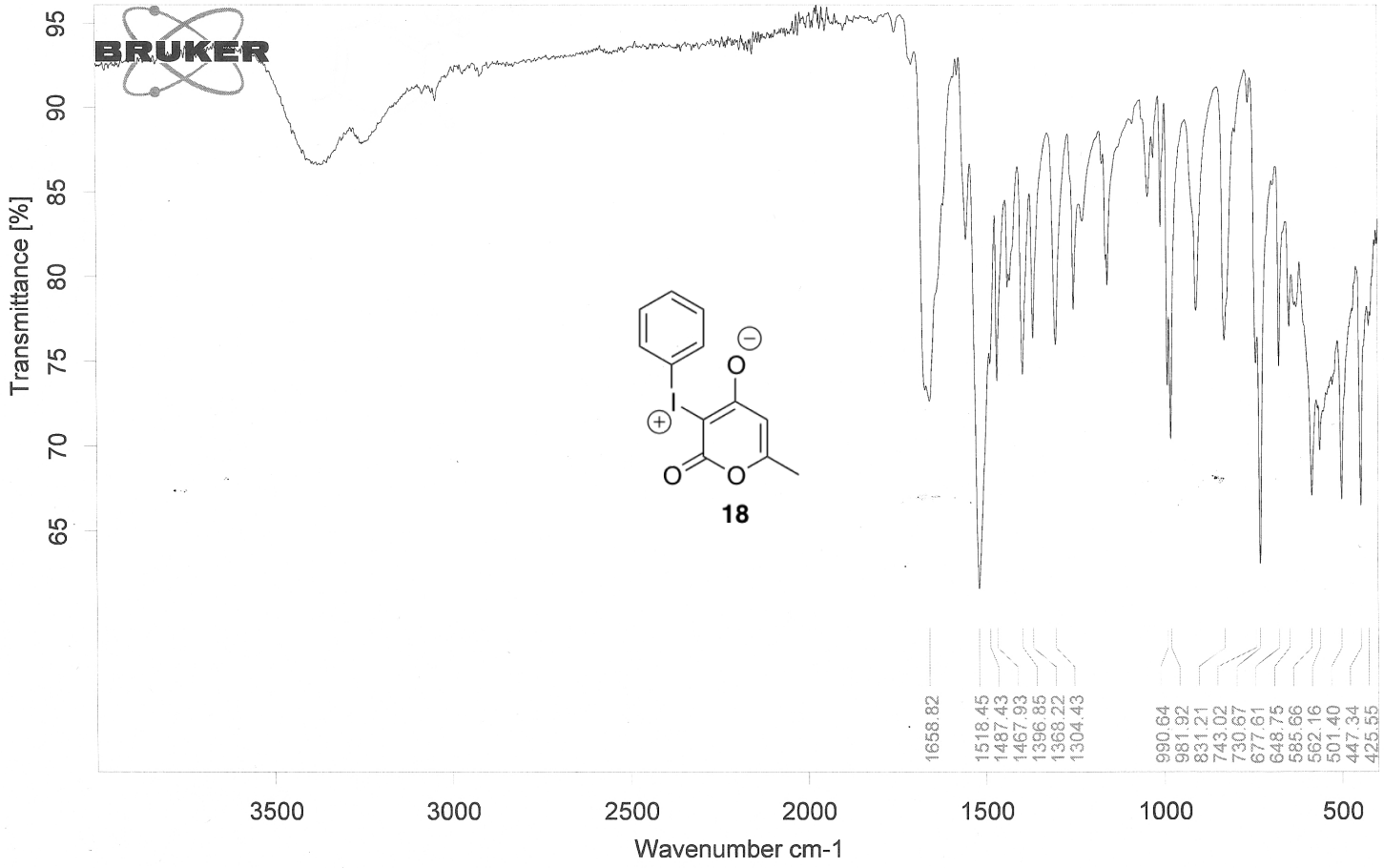

Sample Name:
TES_46_f14
Archive directory:
Sample directory:
FidFile: TES_46_f14_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Nov 20 2013
Sample #15, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.8047115 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
16
7.232
7.213
7.089
7.071
5.856
5.849
5.714
5.708
5.219
3.695
2.129
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.00
-0.00
2.03
1.05
0.98
0.98
1.98
3.00
3.02

Transmittance [%]
95
90
85
80
75
70
65
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
1645.42
1598.44
1529.29
1450.67
1364.39
1342.78
1231.06
1156.21
1053.40
938.07
788.32
749.47
731.15
692.44
639.53
510.26
460.36
Br
O
O
N
17
BRUKER
C:\Users\LabUser\Desktop\Training Day\1Bz3Br4MeOpyridone.0
1Bz3Br4MeOpyridone
film
4/15/2014
Page 1/1


Sample Name:
TES_47_1
Archive directory:
Sample directory:
FidFile: TES_47_1_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Nov 25 2013
Sample #13, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.8047187 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
7.282
7.263
7.240
7.157
7.155
7.153
7.136
7.135
5.920
5.919
5.356
5.277
3.911
2.284
2.282
Br
O
O
N
17
9
8
7
6
5
4
3
2
1
ppm
1.81
1.00
1.94
0.15
2.97
3.00

BRUKER
Transmittance [%]
95
90
85
80
75
70
65
60
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
1627.53
1585.93
1486.14
1451.25
1318.28
1245.91
1198.40
1010.31
1000.59
778.31
770.59
698.00
556.30
476.67
O
N
H
O
I
C:\Users\LabUser\Desktop\Training Day\3Iodo4phenoxypyridone.0
3Iodo4phenoxypyridone
film
4/15/2014
Page 1/1


Sample Name:
TES_8_2_correct
Archive directory:
Sample directory:
FidFile: TES_8_2_correct_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: dmso
Data collected on: Jul 2 2013
Sample #37, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 7225.4 Hz
16 repetitions
OBSERVE H1, 399.8066106 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
7.439
7.099
7.081
5.490
5.488
3.321
2.495
2.491
2.486
2.481
2.476
2.070
2.066
2.064
O
I
O
N
H
12
11
10
9
8
7
6
5
4
3
2
1
ppm



C:\Users\LabUser\Desktop\Training Day\pyoneylide.0 pyoneylide film	4/15/2014

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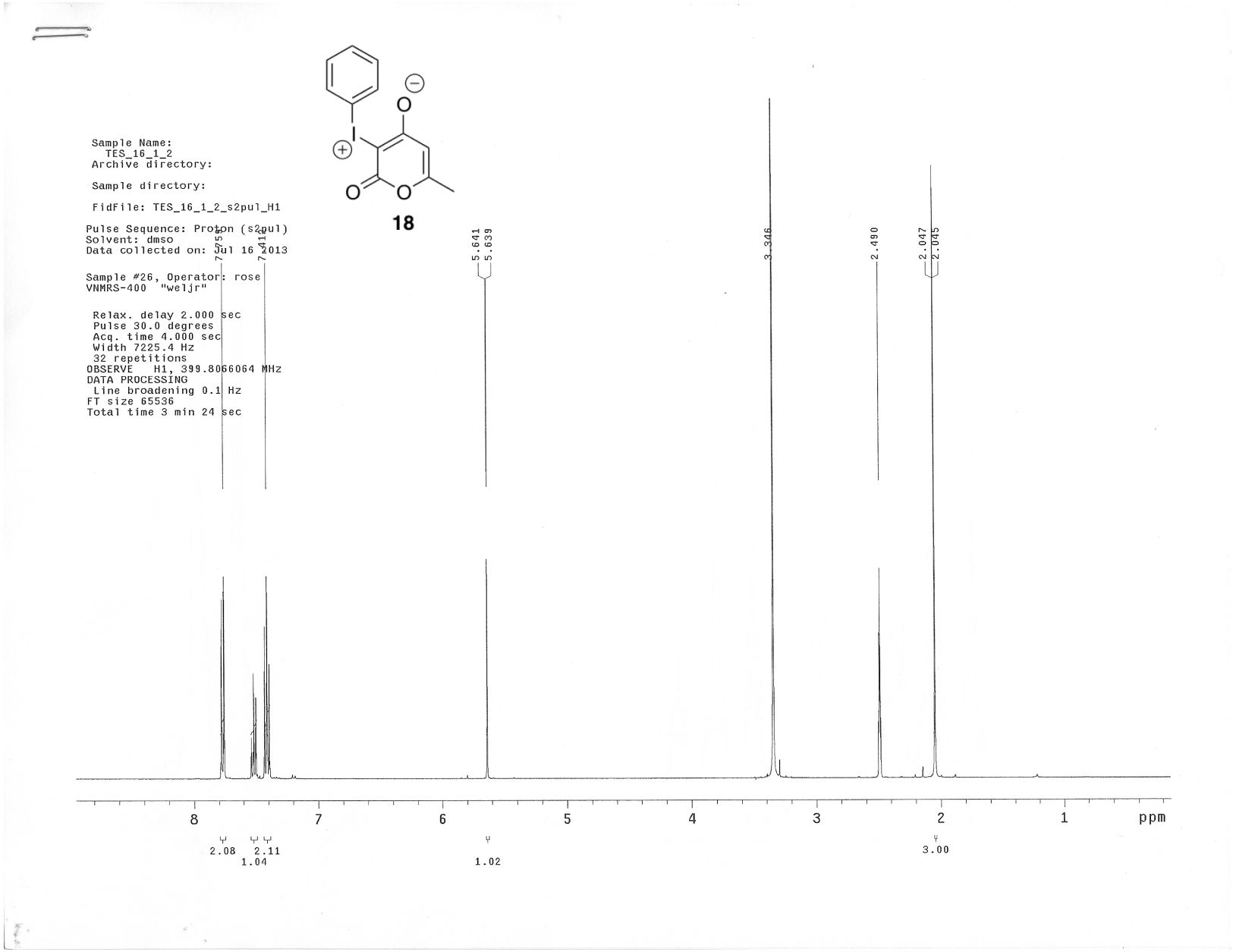
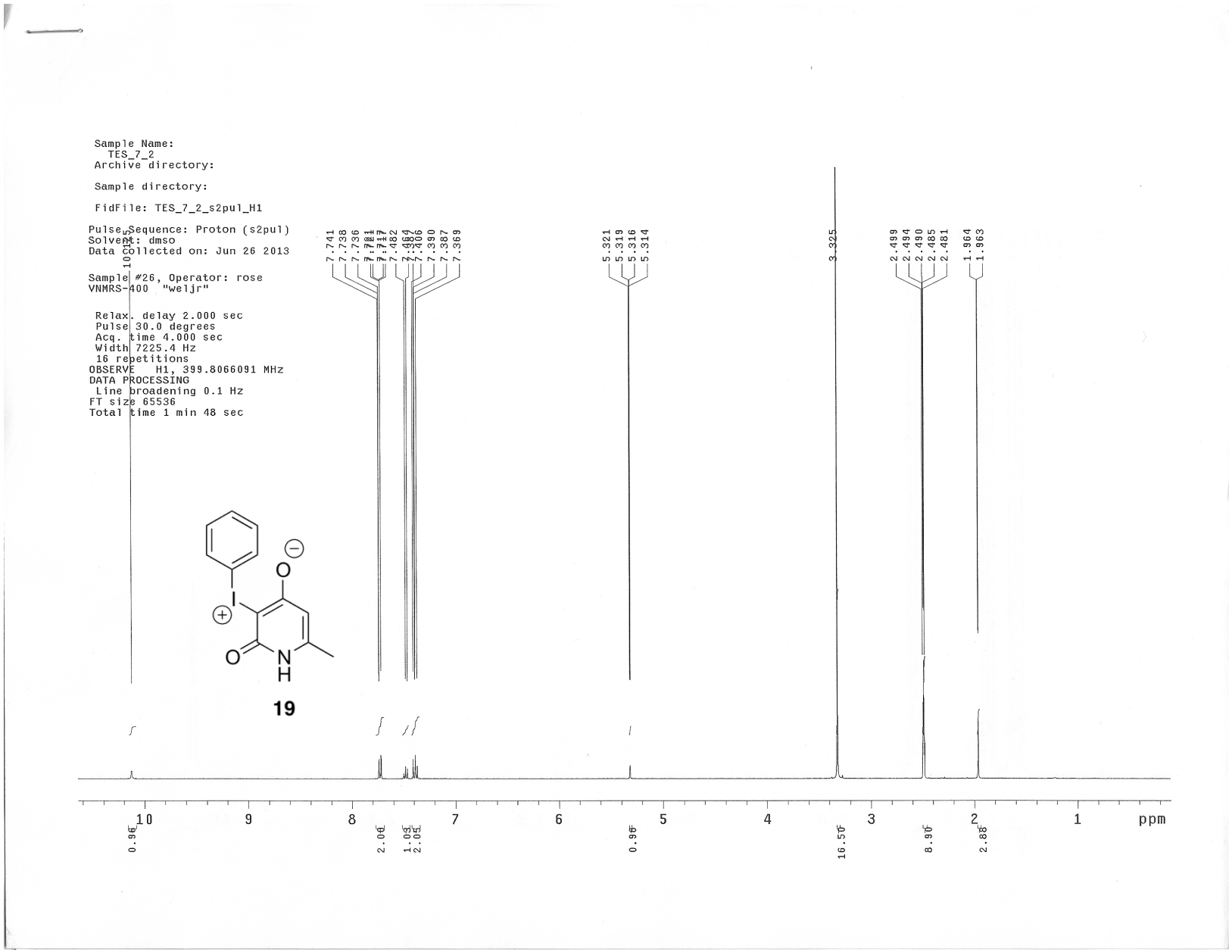
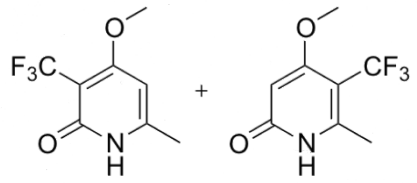

Sample Name:
TES_16_1_2
Archive directory:
Sample directory:
FidFile: TES_16_1_2_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: dmso
Data collected on: Jul 16 2013
Sample #26, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 7225.4 Hz
32 repetitions
OBSERVE H1, 399.8066064 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 3 min 24 sec
18
7.755
7.741
7.411
5.641
5.639
3.346
2.490
2.047
2.045
8
7
6
5
4
3
2
1
ppm
2.08
2.11
1.04
1.02
3.00

Transmittance [%]
95
90
85
80
75
70
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
446.12
521.82
581.94
623.53
733.02
1478.06
1467.64
1598.52
19
C:\Users\LabUser\Desktop\IR Users\Tim\pyridoneylide.0
pyridoneylide
film
4/15/2014
Page 1/1

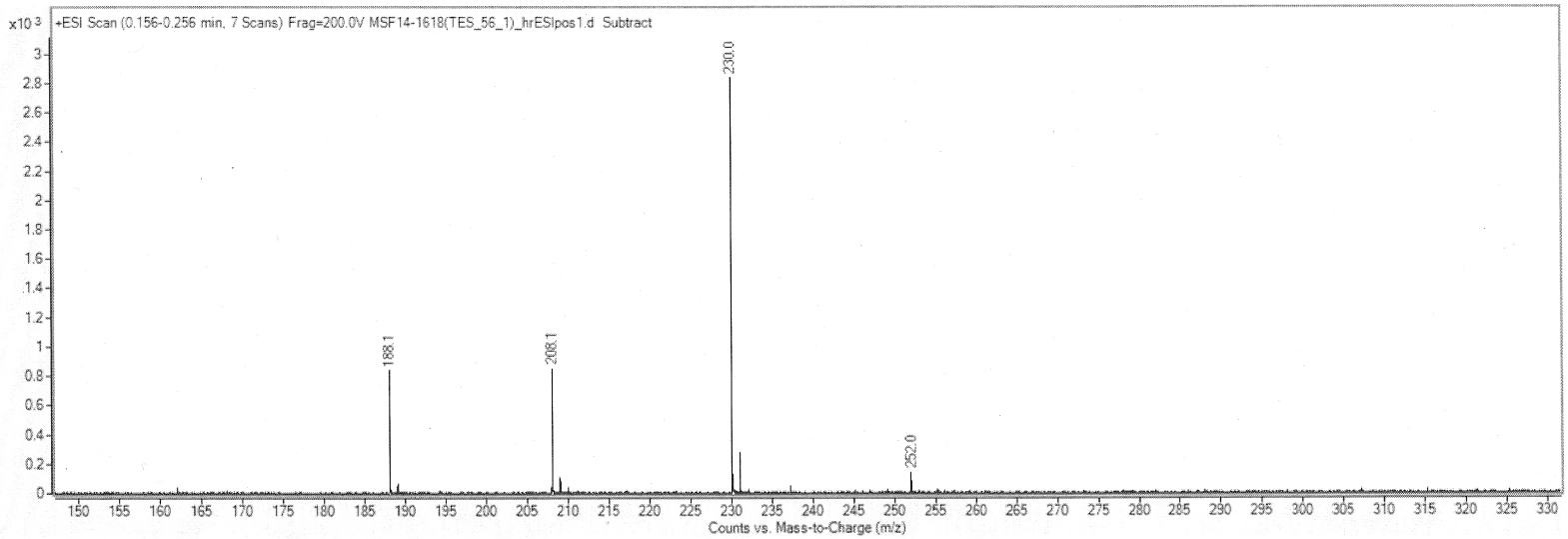

Sample Name:
TES_7_2
Archive directory:
Sample directory:
FidFile: TES_7_2_s2pul_H1
Pulse Sequence: Proton (s2pul)
Solvent: dmso
Data collected on: Jun 26 2013
Sample #26, Operator: rose
VNMRS-400 "weljr"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 7225.4 Hz
16 repetitions
OBSERVE H1, 399.8066091 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec
10.146
7.741
7.738
7.736
7.482
7.406
7.390
7.387
7.369
5.321
5.319
5.316
5.314
3.325
2.499
2.494
2.490
2.485
2.481
1.964
1.963
19
0.96
2.00
1.05
2.05
0.96
16.50
8.90
2.88
10
9
8
7
6
5
4
3
2
1
ppm

Transmittance [%]
100
95
90
85
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
1646.94
1476.97
1354.50
1104.00
1034.61
20
C:\Users\LabUser\Desktop\Training Day\3-CF3-4MeO-NH-pyridone.1
3-CF3-4MeO-NH-pyridone
film
3/28/2014
Page 1/1

Transmittance [%]
100
90
80
70
60
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
1677.02
1367.68
1312.00
1257.78
1235.33
1213.66
1181.60
1123.31
1096.08
1038.60
BRUKER
CF3
O
N
H
O
21
C:\Users\LabUser\Desktop\Training Day\5-CF3-4MeO-NH-pyridone.0
5-CF3-4MeO-NH-pyridone
film
3/28/2014
Page 1/1


O
F3C
O
N
H
+
O
CF3
O
N
H

20 **21**


x10 3
+ESI Scan (0.156-0.256 min, 7 Scans) Frag=200.0V MSF14-1618(TES_56_1)_hrESIpos1.d Subtract
230.0
188.1
208.1
252.0
Counts vs. Mass-to-Charge (m/z)

Sample Name:
TES_55_2
Archive directory:

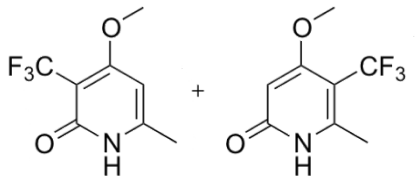
Sample directory:

FidFile: TES_55_2_01

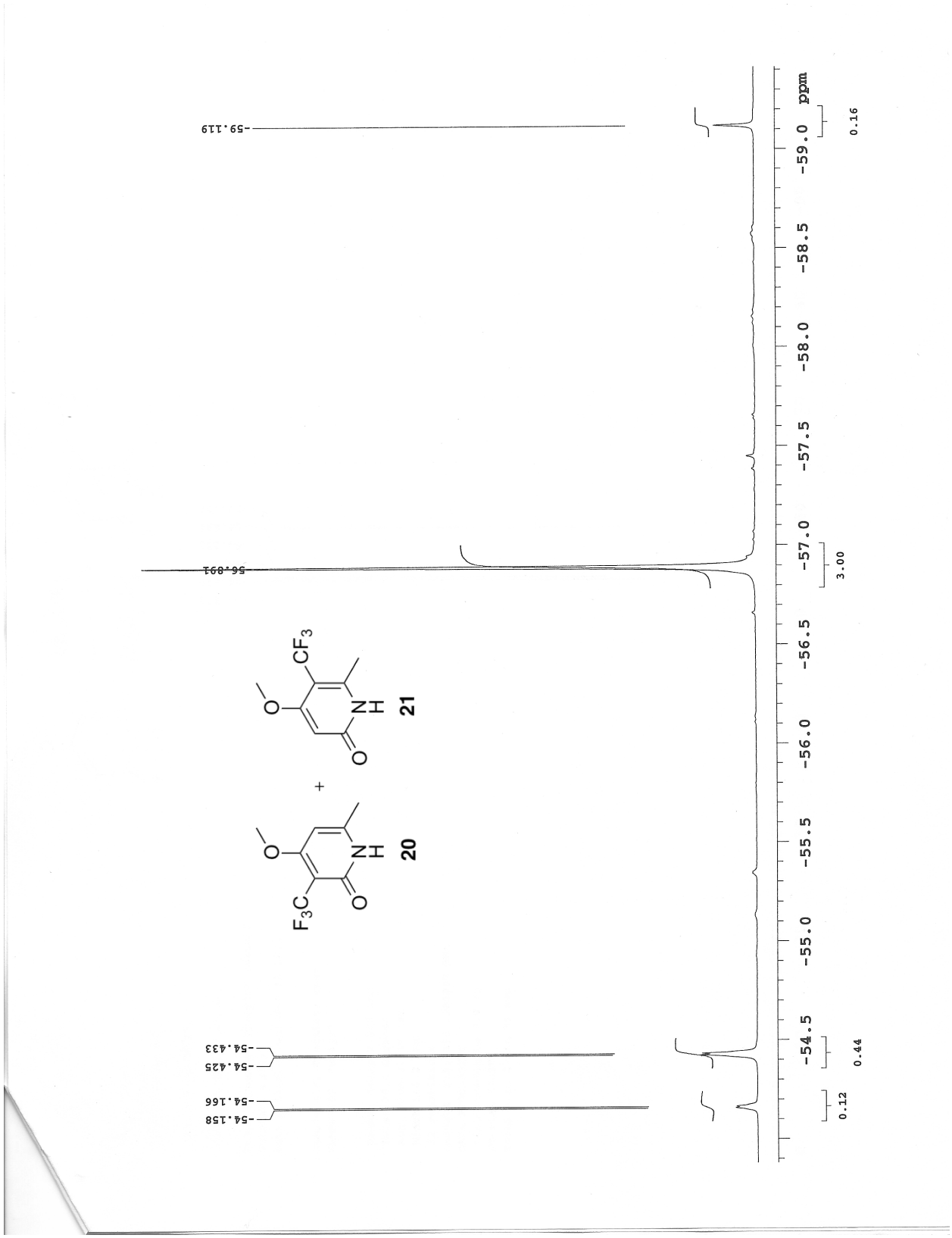
Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Mar 21 2014

Sample #4, Operator: rose
VNMRS-400 "weljr"

Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 2802.7 Hz
16 repetitions
OBSERVE H1, 399.8047189 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec



20 **21**


-59.119
-56.891
-54.433
-54.425
-54.166
-54.158
21
20
+
ppm
-54.5
-55.0
-55.5
-56.0
-56.5
-57.0
-57.5
-58.0
-58.5
-59.0
0.12
0.44
3.00
0.16

Sample Name:
TES_60_1wide
Archive directory:

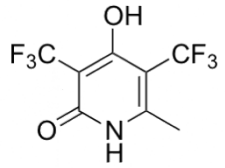
Sample directory:

FidFile: TES_60_1wide_01

Pulse Sequence: Proton (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2014

Sample #16, Operator: rose
VNMRS-400 "weljr"

Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 8012.8 Hz
16 repetitions
OBSERVE H1, 399.8047107 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 min 48 sec



22

Sample Name:
TES_60_1f
Archive directory:

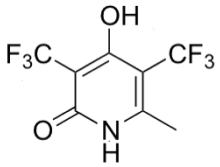
Sample directory:

FidFile: TES_60_1f_01

Pulse Sequence: Fluorine (s2pul)
Solvent: cdcl3
Data collected on: Apr 3 2014

Sample #16, Operator: rose
VNMRS-400 "weljr"

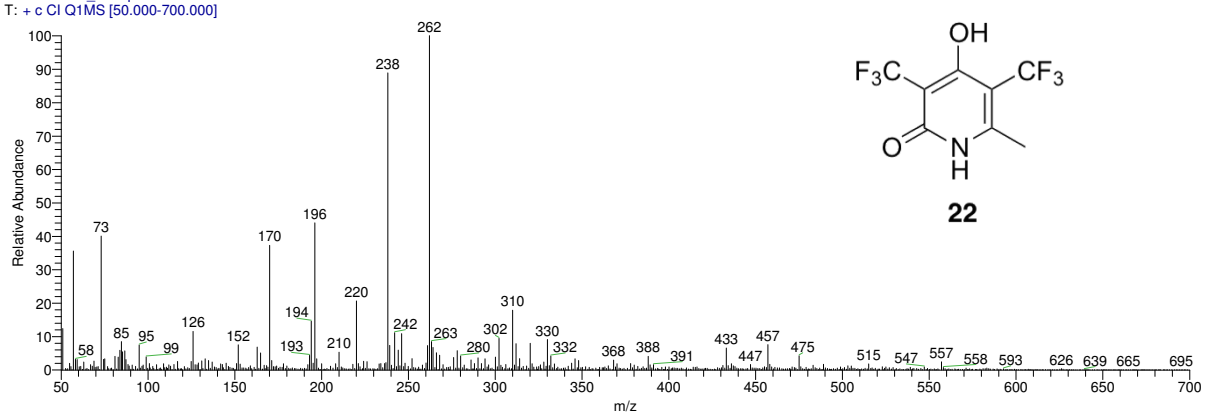
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 2.517 sec
Width 104.2 kHz
32 repetitions
OBSERVE F19, 376.1922892 MHz
DATA PROCESSING
Line broadening 2.0 Hz
FT size 524288
Total time 2 min 34 sec



22

C:\Xcalibur\...\MSF14-1619_LRCIpos1 5/6/2014 10:14:25 TES_60

MSF14-1619_LRCIpos1 #57-62 RT: 0.21-0.23 AV: 6 NL: 3.51E7
T: + c CI Q1MS [50.000-700.000]



22

MSF14-1619_LRCIpos1 #57-62 RT: 0.21-0.23 AV: 6 NL: 3.51E7
T: + c CI Q1MS [50.000-700.000]